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(54) **SHEAR STRESS-RESPONSE DNA**

(57) This invention relates to a novel shear stress-responsive DNA, a protein encoded by the DNA, an antibody against the protein, a method for detecting a shear stress-responsive DNA or protein, a therapeutic

agent and a diagnostic agent for vascular diseases caused by arteriosclerosis and a method for screening the therapeutic agent and the diagnostic agent.

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DescriptionField of the Invention

5 **[0001]** This invention relates to novel DNAs obtained by employing the subtraction method while paying attention to mRNAs which show a shear stress-dependent increase of expression in vascular endothelial cells; and proteins encoded by these DNAs. Moreover, this invention also relates to antibodies against the proteins; methods for detecting the proteins and the DNAs; and the diagnosis and treatment of various vascular diseases caused by arteriosclerosis, such as cardiac insufficiency, restenosis after PTCA (percutaneous transluminal coronary angioplasty) and hypertension, and methods for screening an agent for such treatment or diagnosis.

Background of the Invention

15 **[0002]** Conventionally, vascular endothelial cells covering the inner surfaces of blood vessels in the form of a monolayer have been considered to be a mere lining for separating the vascular tissue from blood flowing through the lumen of the blood vessel. However, as a result of the recent progress of research on the vascular endothelium, it has been found that the endothelium has a great diversity of functions which are very important for the living body. These functions include, for example, regulation of the material permeability between blood and tissue, regulation of the tension of the blood vessel, maintenance of an antithrombogenic activity, control of the proliferation of smooth muscle, repair of tissues, inflammatory reaction, and remodeling of the blood vessel. The physical force applied to the vascular wall by a flow of blood is called a shear stress, which is defined by the flow velocity of blood, the viscosity of blood, and the diameter and morphology of the blood vessel. The shear stress acts on the endothelium covering the inner surface of the vascular wall and distorts vascular endothelial cells in the direction of the blood flow. According to investigations made for the last ten years or so, it has been revealed that, similarly to chemical stimuli such as hormones and cytokines, this physical stimulus is closely associated with the morphology of vascular endothelial cells and regulation of the above-described various functions [Cell Technology (in Japanese), 16, 950(1997)].

20 **[0003]** In industrially advanced countries including Japan, atherosclerosis is one of the major causes of death of adults. It is known that the malfunction of blood vessels caused by hypercholesterolemia, hyperhomocysteinemia, diabetes mellitus and the like is closely related to the development of atherosclerosis and the aggravation of the morbid state [Molecular Cardiovascular Medicine, 49-61(1995)]. On the other hand, it is also known that arteriosclerotic lesions are not uniformly distributed over all blood vessels, but are localized in specific regions such as the outside of a bend in a branched part of a blood vessel. Since such local development is also observed in experimental animal having a genetically increased blood cholesterol level, it is considered that the incorporation of cholesterol into the vascular endothelium occurs in two stages, i.e., local changes of vascular endothelial cells and the actual incorporation of cholesterol [Arterioscler. Thromb., 14, 133-140(1994)]. The cause of such local development has scarcely been clarified. However, since incipient lesions occur frequently in places where the intensity and direction of a shear stress are not steady, i.e., places where a low shear stress is produced and the separation or stagnation of a flow or turbulence (e.g., eddies) tends to occur, hemodynamic stresses such as shear stresses are considered to be closely related to the development of atherosclerosis. At present, the molecular mechanism by which a shear stress induces arteriosclerosis locally is not clearly understood. However, genes whose expression is altered by applying a shear stress mechanically to vascular endothelial cells cultured *in vitro* have been searched until now. Thus, it has been found that a shear stress activates various transcription factors such as AP(activator protein)-1 and NF(nuclear factor)- κ B, and thereby causes a change of expression of genes under the control of these transcription factors. Up to now, it has been reported that the proteins encoded by genes exhibiting an alteration of expression in response to a shear stress stimulus include growth factors such as PDGF (platelet-derived growth factor) and TGF(transforming growth factor)- β ; adhesion factors such as VCAM(vascular cell adhesion molecule)-1 and ICAM(intercellular adhesion molecule)-1; tension control factors such as ET(endothelin)-1; thrombolysis factors such as t-PA (tissue-type plasminogen activator); enzymes such as NOS (nitric oxide synthase) 3, COX (cyclooxygenase) 2 and SOD (superoxide dismutase); and the like [Molecular Medicine Today, 5, 40(1999)]. Thus, the genes responding to a shear stress in an *in vitro* reconstituted system are believed to include two groups of molecules having different characteristics, i.e., arteriosclerosis induction factors considered to be expressed in at least low shear stress regions of blood vessels in response to a change of shear stress, and molecules suppressing the development of arteriosclerosis in intravascular places where a high shear stress is produced constitutively. However, among the genes presumed to exhibit an alteration of expression in response to a shear stress only some genes have been specifically identified. In order to understand the cause of arteriosclerosis and develop methods for the prevention and treatment thereof, it is necessary to clarify unknown genes responding to a shear stress. In recent years, unknown genes responding to a shear stress have been searched by employing the differential display method or the like, but it involves several problems in that genes whose alteration of expression is of the order of several times cannot be easily obtained and in that the proportion of false positive clones is high [Nucleic

Acids Res., 23, 4520-4523(1995)]. Consequently, the number of genes exhibiting an alteration of expression in response to a shear stress and clarified by the differential display method is not great [Proc. Natl. Acad. Sci. USA, 93, 10417-10422(1996); Proc. Natl. Acad. Sci. USA, 94, 9314-9319(1997); Biochem. Biophys. Res. Comm., 255, 347-351 (1996); Biochem. Biophys. Res. Comm., 246, 881-887(1998); US Patent 5,834,248 (1998); US Patent 5,849,578 (1998); US Patent 5,882,925 (1999)].

[0004] As described above, it is recognized that changes of the shear stress applied to vascular endothelial cells are involved in the local development of atherosclerosis, but the fact is that its molecular mechanism is scarcely understood. Nevertheless, it has been reported for long that a shear stress reduces the turnover of endothelial cells *in vivo*, i.e., a shear stress acts so as to suppress the cell death of the endothelium [Atherosclerosis, 17, 401-417(1973); Circ. Res., 69, 1557-1565(1991)]. Moreover, there are many reports showing that, *in vitro*, the apoptosis of endothelial cells induced by TNF- α stimulation, hydrogen peroxide stimulation, growth factor depletion or the like is markedly suppressed by the application of a shear stress [J. Exp. Med., 185, 601-607(1997); FEBS Lett., 399, 71-74(1997); Arterioscler. Thromb. Vas. Biol., 17, 3588-3592(1997); Biochem. Biophys. Res. Commun., 231, 586-590(1997)]. That is, it is believed that, in branched or curved parts of arteries where a low shear stress is produced, the character of endothelial cells changes so as to induce apoptosis and this is a cause defining the locality of an incipient arteriosclerotic lesion. At present, however, little is known about genes participating in the molecular mechanism by which the application of a shear stress suppresses the apoptosis of endothelial cells, namely the signal transduction mechanism.

[0005] The understanding of the molecular mechanism by which vascular endothelial cells respond to a shear stress leads us to learn the mechanism of development of various vascular diseases caused by arteriosclerosis, and the target for treatment. In order to elucidate the signal transduction mechanism, it is necessary to obtain a group of genes which exhibit a shear stress stimulus-dependent alteration of expression in vascular endothelial cells.

[0006] Moreover, the understanding of the molecular mechanism by which the apoptosis of vascular endothelial cells is suppressed in response to a shear stress stimulus leads us to elucidate the mechanism of the local formation of an early lesion of arteriosclerosis and thereby discover remedies for various vascular diseases caused by arteriosclerosis. In order to elucidate the molecular mechanism, it is necessary to obtain genes which exhibit a shear stress stimulus-dependent increase of expression in vascular endothelial cells and have an apoptosis-suppressing activity.

Summary of the Invention

[0007] The present inventors made intensive investigations with a view to solving the above-described problems and have now obtained the following results. Specifically, mRNA derived from cultured vascular endothelial cells having a shear stress applied thereto was used as a template to prepare a cDNA library, and mRNA extracted from endothelial cells having no shear stress applied thereto was subtracted therefrom. Thus, a subtraction library was constructed in which genes exhibiting an increase of expression under shear stress-applied conditions was concentrated. However, since abundance of genes having a low amount of expression are equalized and empty vectors having no inserted fragment are increased in this subtraction library, a reverse subtraction method was newly developed to construct a second-generation subtraction library in which genes exhibiting an alteration of expression in response to a shear stress were concentrated from the subtraction library. Clones present in this second-generation subtraction library were randomly subjected to Northern hybridization, so that a large number of clones exhibiting an increase of expression by the application of a shear stress were obtained. Among these clones, not only the genes already known to exhibit an alteration of expression in response to a shear stress, but also genes presumed to act on the regulation of arteriosclerosis, genes which have not yet been known to be associated with arteriosclerosis, and novel genes were found. Furthermore, peptides encoded by these genes were found. Thus, the present invention has been completed.

[0008] Specifically, the present invention provides the following (1) to (7).

(1) A DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO: 143, 145, 147, 149, 151, 153, 155, 157, 168, 170 and 172.

(2) A shear stress-responsive DNA capable of hybridizing with a DNA having the nucleotide sequence represented by SEQ ID NO:143, 145, 149, 151, 153, 155, 157, 168, 170 or 172 under stringent conditions.

(3) A shear stress-responsive DNA capable of hybridizing with a DNA having the nucleotide sequence represented by SEQ ID NO:147 under stringent conditions, and having not less than 90% homology with the DNA.

(4) A DNA having the same sequence as 5 to 60 consecutive bases in a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:143, 145, 149, 153, 155, 157, 168, 170 and 172, or a DNA having a sequence complementary to the DNA.

(5) A method for detecting an mRNA for a shear stress-responsive gene using a DNA according to any of (1) to (4).

(6) A diagnostic agent for vascular diseases caused by arteriosclerosis which contains a DNA according to any of (1) to (4).

(7) A method for detecting a gene causative of arteriosclerosis using a DNA according to any of (1) to (4).

(8) A method for screening an agent for regulating the transcription or translation of a shear stress-responsive gene using a DNA according to any of (1) to (4).

(9) A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using a DNA according to any of (1) to (4).

5 (10) A therapeutic agent for vascular diseases caused by arteriosclerosis which contains a DNA according to any of (1) to (4).

(11) A recombinant virus vector containing a DNA according to any of (1) to (4).

(12) A recombinant virus vector containing an RNA comprising a sequence homologous with the sense strand of a DNA according to any of (1) to (4).

10 (13) A DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO: 111, 113, 115, 116, 117, 119, 121, 123, 125, 127, 129, 130, 131, 132, 133, 134, 135, 137, 139 and 141.

(14) A shear stress-responsive DNA capable of hybridizing with the DNA according to (13) under stringent conditions.

15 (15) A DNA having the same sequence as 5 to 60 consecutive bases in a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO: 111, 113, 115, 116, 117, 119, 121, 123, 125, 127, 129, 130, 131, 132, 133, 134, 135, 137, 139 and 141, or a DNA having a sequence complementary to the DNA.

(16) A diagnostic agent for vascular diseases caused by arteriosclerosis which contains a DNA according to any of (13) to (15).

(17) A method for detecting a gene causative of arteriosclerosis using a DNA according to any of (13) to (15).

20 (18) A method for screening an agent for regulating the transcription or translation of a shear stress-responsive gene using a DNA according to any of (13) to (15).

(19) A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using a DNA according to any of (13) to (15).

25 (20) A method for detecting an mRNA for a shear stress-responsive gene using a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.

30 (21) A method for identifying the apoptosis sensitivity of cells by detecting the endogenous transcription level of a DNA having the nucleotide sequence represented by SEQ ID NO: 7 using a DNA having the nucleotide sequence represented by SEQ ID NO: 7 or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO: 7.

35 (22) A method for suppressing or promoting the apoptosis of cells by regulating the endogenous transcription or translation of a DNA having the nucleotide sequence represented by SEQ ID NO: 7 using a DNA having the nucleotide sequence represented by SEQ ID NO: 7 or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO: 7, or an antisense DNA having a nucleotide sequence complementary to the nucleotide sequence of each of these DNAs.

40 (23) A diagnostic agent for vascular diseases caused by arteriosclerosis which contains a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.

(24) An agent for identifying the apoptosis sensitivity of cells which contains a DNA having the nucleotide sequence represented by SEQ ID NO: 7, or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO: 7.

45 (25) A method for screening an agent for regulating the transcription or translation of a shear stress-responsive gene using a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.

50 (26) A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.

(27) A method for screening an agent for suppressing or promoting the apoptosis of cells by regulating the endogenous transcription or translation of a DNA having the nucleotide sequence represented by SEQ ID NO: 7 using a DNA having the nucleotide sequence represented by SEQ ID NO: 7 or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO: 7.

55 (28) A therapeutic agent for vascular diseases caused by arteriosclerosis which contains a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81,

83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.

(29) An agent for suppressing or promoting the apoptosis of cells which contains a DNA having the nucleotide sequence represented by SEQ ID NO:7 or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7, or an antisense DNA having a nucleotide sequence complementary to the nucleotide sequence of each of these DNAs.

(30) A recombinant virus vector containing a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.

(31) A recombinant virus vector containing an RNA comprising a sequence homologous with the sense strand of a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.

(32) A therapeutic agent for vascular diseases caused by arteriosclerosis which contains a recombinant virus vector according to (30) or (31).

(33) A method for suppressing the apoptosis of cells using a recombinant virus vector containing a DNA having the nucleotide sequence represented by SEQ ID NO:7, or a recombinant virus vector containing an RNA comprising a sequence homologous with the sense strand of a DNA having the nucleotide sequence represented by SEQ ID NO:7.

(34) A method for screening an agent for suppressing or promoting the apoptosis of cells using a recombinant virus vector containing a DNA having the nucleotide sequence represented by SEQ ID NO:7, or a recombinant virus vector containing an RNA comprising a sequence homologous with the sense strand of a DNA having the nucleotide sequence represented by SEQ ID NO:7.

(35) A protein having an amino acid sequence selected from the amino acid sequences represented by SEQ ID NO:144, 146, 148, 150, 152, 154, 156, 158, 169, 171 and 173.

(36) A protein comprising an amino acid sequence in which one or more amino acids are deleted, replaced or added as compared with the amino acid sequence possessed by the protein according to (35), and having an activity participating in the formation of an arteriosclerotic lesion.

(37) A DNA encoding a protein according to (35) or (36).

(38) A recombinant DNA obtained by inserting a DNA according to any of (1)-(4) and (37) into a vector.

(39) A transformant obtained by introducing the recombinant DNA according to (38) into a host cell.

(40) A process for the preparation of a protein which comprises culturing the transformant according to (39) in a culture medium, causing a protein according to (35) or (36) to be produced and accumulated in the culture medium, and harvesting the protein from the resulting culture.

(41) A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis which comprises culturing the transformant according to (39) in a culture medium and using the resulting culture for the screening.

(42) A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using a protein according to (35) or (36).

(43) A recombinant virus vector capable of producing a protein according to (35) or (36).

(44) A therapeutic agent for vascular diseases caused by arteriosclerosis which contains the recombinant virus vector of (43).

(45) An antibody capable of recognizing a protein according to (35) or (36).

(46) A method for detecting a protein according to (35) or (36) immunologically using the antibody according to (45).

(47) A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using the antibody according to (45).

(48) A method for screening an agent for regulating the transcription or translation of a shear stress-responsive gene using the antibody according to (45).

(49) A diagnostic agent for vascular diseases caused by arteriosclerosis which contains the antibody according to (45).

(50) A therapeutic agent for vascular diseases caused by arteriosclerosis which contains the antibody according to (45).

(51) A drug delivery method which comprises combining the antibody of (45) with a radioactive isotope, a protein or a low-molecular-weight agent, and delivering the resulting conjugated antibody to an arteriosclerotic lesion.

(52) An antibody capable of recognizing a protein having an amino acid sequence represented by SEQ ID NO: 112, 114, 118, 120, 122, 124, 126, 128, 136, 138, 140 and 142.

(53) A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using the antibody according to (52).

(54) A method for screening an agent for suppressing the transcription or translation of a shear stress-responsive

gene using the antibody according to (52).

(55) A diagnostic agent for vascular diseases caused by arteriosclerosis which contains the antibody according to (52).

(56) A therapeutic agent for vascular diseases caused by arteriosclerosis which contains the antibody according to (52).

(57) A drug delivery method which comprises combining the antibody of (52) with a radioactive isotope, a protein or a low-molecular-weight agent, and directing the resulting conjugated antibody to an arteriosclerotic lesion.

(58) A method for screening an agent capable of binding specifically to a protein having the amino acid sequence represented by SEQ ID NO:8 and effective for suppressing or promoting the apoptosis of cells, using a protein having the amino acid sequence represented by SEQ ID NO:8.

(59) A method for screening an agent for suppressing or promoting the apoptosis of cells which comprises inserting a DNA having the nucleotide sequence represented by SEQ ID NO:7 or a DNA encoding a protein having the amino acid sequence represented by SEQ ID NO:8, into a vector; introducing the resulting recombinant DNA into a host cell; culturing the resulting transformant in a culture medium; and using the resulting culture for the screening.

(60) A recombinant virus vector capable of producing a protein having an amino acid sequence selected from the amino acid sequences represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 and 110.

(61) A therapeutic agent for vascular diseases caused by arteriosclerosis which contains the recombinant virus vector of (60).

(62) A method for suppressing the apoptosis of cells using a recombinant virus vector capable of producing a protein having the amino acid sequence represented by SEQ ID NO:8.

(63) An agent for suppressing the apoptosis of cells which contains a recombinant virus vector capable of producing a protein having the amino acid sequence represented by SEQ ID NO:8.

(64) A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 or 110.

(65) A method for screening an agent for suppressing or promoting the transcription or translation of a shear stress-responsive gene using an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 or 110.

(66) A method for regulating the apoptosis of cells using an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.

(67) A method for screening an agent for regulating the apoptosis of cells using an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.

(68) A method for identifying the apoptosis sensitivity of cells by detecting the expression level of a protein having the amino acid sequence represented by SEQ ID NO:8 using an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.

(69) A method according to any of (21), (22), (27), (33), (34), (58), (59), (62), (66), (67) and (68) wherein the cells are vascular endothelial cells.

(70) A diagnostic agent for vascular diseases caused by arteriosclerosis which contains an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 or 110.

(71) An agent for identifying the apoptosis sensitivity of cells which contains an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.

(72) A therapeutic agent for vascular diseases caused by arteriosclerosis which contains an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 or 110.

(73) An agent for regulating the apoptosis of cells which comprises an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.

(74) An agent for suppressing or promoting the apoptosis of cells which is obtained by a method according to any of (27), (34), (58), (59) and (67).

(75) An agent according to any of (24), (29), (63), (71), (73) and (74) wherein the cells are vascular endothelial cells.

(76) A drug delivery method which comprises combining an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36,

38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 or 110, with a radioactive isotope, a protein or a low-molecular-weight agent, and directing the resulting conjugated antibody to an arteriosclerotic lesion.

[0009] The term "regulate" as used herein means the action of suppressing or promoting. Moreover, the term "agent" refers to any substances having an arbitrary molecular weight such as proteins and nucleic acids.

[0010] The DNA of the present invention is a shear stress-responsive DNA. Examples thereof include a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:143, 145, 147, 149, 151, 153, 155, 157, 168, 170 and 172; and a DNA capable of hybridizing with the foregoing DNAs under stringent conditions and showing an alteration in the expression level in response to the application of a shear stress.

[0011] The above-described DNA capable of hybridizing with a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:143, 145, 147, 149, 151, 153, 155, 157, 168, 170 and 172 under stringent conditions is a DNA obtained by carrying out colony hybridization, plaque hybridization or Southern blot hybridization while using a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO: 143, 145, 147, 149, 151, 153, 155, 157, 168, 170 and 172 as a probe. Specifically, it includes DNA which can be identified by using a filter having colony- or plaque-derived DNAs immobilized thereon to carry out hybridization at 65°C in the presence of 0.7-1.0 M NaCl, and then washing the filter with an SSC solution having a 0.1 - to 2-fold concentration (an SSC solution having a one-fold concentration is composed of 150 mM sodium chloride and 15 mM sodium citrate) under 65°C conditions.

[0012] Hybridization may be carried out according to the methods described in Molecular Cloning, A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press (1989) (hereinafter referred to briefly as "Molecular Cloning, Second Edition"); Current Protocols in Molecular Biology, John Wiley & Sons (1987-1997) (hereinafter referred to briefly as "Current Protocols in Molecular Biology"); DNA Cloning 1: Core Techniques, A Practical Approach, Second Edition, Oxford University (1995); and the like. Specific examples of the hybridizable DNAs include DNAs having not less than 60% homology, preferably not less than 80% homology, more preferably not less than 90% homology, and most preferably not less than 95% homology with a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:143, 145, 147, 149, 151, 153, 155, 157, 168, 170 and 172.

[0013] Furthermore, the DNA of the present invention also includes oligonucleotides and antisense oligonucleotide having a sequence of a part of the DNA of the present invention. The oligonucleotide includes, for example, an oligonucleotide having the same sequence as the nucleotide sequence of 5 to 60 residues, preferably 10 to 40 residues, in a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:143, 145, 147, 149, 151, 153, 155, 157, 168, 170 and 172. The antisense oligonucleotide includes, for example, an antisense oligonucleotide of the foregoing oligonucleotide.

[0014] The protein of the present invention includes a protein having an activity associated with arteriosclerosis. Specific examples thereof include a protein having an amino acid sequence selected from the amino acid sequences represented by SEQ ID NO:144, 146, 148, 150, 152, 154, 156, 158, 169, 171 and 173, and a protein comprising amino acid sequences in which one or more amino acids are deleted, replaced or added as compared with the amino acid sequence possessed by the foregoing protein, and having an activity involved in the formation of an arteriosclerotic lesion.

[0015] The protein comprising amino acid sequence in which one or more amino acids are deleted, replaced or added as compared with the amino acid sequence of protein having an amino acid sequence selected from the amino acid sequences represented by SEQ ID NO:144, 146, 148, 150, 152, 154, 156, 158, 169, 171 and 173, and having an activity involved in the formation of an arteriosclerotic lesion may be prepared according to the methods described in Molecular Cloning, Second Edition; Current Protocols in Molecular Biology; Nucleic Acids Research, 10, 6487(1982); Proc. Natl. Acad. Sci. USA, 79, 6409(1982); Gene, 34, 315(1985); Nucleic Acids Research, 13, 4431(1985); Proc. Natl. Acad. Sci. USA, 82, 488(1985); and the like.

[0016] Moreover, among the acquired large number of genes exhibiting an increase of expression by the application of a shear stress in vascular endothelial cells, the present inventors have found A4RS-041 having homology with LFG (lifeguard), a brain-specific gene which has been reported to suppress Fas-mediated apoptosis [Proc. Natl. Acad. Sci. USA, 22, 12673-12678(1999)]. First of all, according to an analysis of the nucleotide sequence of A4RS-041, the present inventors have found that A4RS-041 is a gene entirely different from LFG because A4RS-041 has about 50% identity to LFG, but about one-third thereof on the amino-terminal side has little homology. Moreover, the present inventors have also found that the expression profiles of A4RS-041 and LFG in tissues are substantially different because A4RS-041 is widely expressed in a variety of tissues including vascular endothelial cells, whereas LFG is highly expressed in the brain but not in vascular endothelial cells. Furthermore, by constructing a transformed cell which permits A4RS-041 to be stably and highly expressed, the present inventors have also found that A4RS-041 suppresses Fas-mediated apoptosis, thus ascertaining that A4RS-041 is a key molecule for the suppression of the apoptosis of vascular endothelial cells by a shear stress. Thus, the present invention has been completed.

Brief Description of the Drawings

[0017]

FIG. 1 illustrates the results of Northern analysis of genes exhibiting an increase of expression in response to a shear stress stimulus. Lanes 1-41 show shear stress-dependent increases of expression for A4RS-016, -026, -040, -041, -063, -096, -116, -126, -131, -148, -154, -174, -175, -194, -197, -260, -271, -307, -355, -389, -391, -423, -431, -453, -492, -507, -514, -523, -544, -547, -557, -577, -588, -602, -608, -612, -625, -666, -668, -674 and -682, respectively. In each blot, 4 µg of total RNA derived from HUVEC having no shear stress applied thereto (with a stimulation time of 0) was electrophoresed in the left-hand lane, and 4 µg of total RNA derived from HUVEC having a shear stress applied thereto (a mixture of equal amounts of total RNA samples derived from HUVEC stimulated for 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 20 hours) was electrophoresed in the right-hand lane.

FIG. 2 illustrates the results of Northern analysis of genes exhibiting an increase of expression in response to a shear stress stimulus. Lanes 42-83 show shear stress-dependent increases of expression for A4RS-751, -781, -784, -817, -818, -914, -929, -935, -938, -939, -945, -947, -948, -949, -011, -115, -143, -171, -193, -280, -402, -533, -604, -615, -619, -626, -676, -679, -737, -780, -826, -916, -933, -943, -002, -049, -230, -239, -242, -491, -578 and -829, respectively. In each blot, 4 µg of total RNA derived from HUVEC having no shear stress applied thereto (with a stimulation time of 0) was electrophoresed in the left-hand lane, and 4 µg of total RNA derived from HUVEC having a shear stress applied thereto (a mixture of equal amounts of total RNA samples derived from HUVEC stimulated for 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 20 hours) was electrophoresed in the right-hand lane.

FIG. 3 illustrates the results of Northern blotting analysis of genes expressed in response to a shear stress stimulus, showing their changes of expression with time. Lanes 1-17 show shear stress-dependent increases of expression for A4RS-016, -041, -063, -096, -116, -260, -271, -307, -389, -391, -602, -784, -115, -143, -193, -280 and -402, respectively. In each blot, 4 µg of total RNA samples derived from HUVEC having shear stress application times of 0, 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 20 hours respectively were electrophoresed as viewed from left to right.

FIG. 4 illustrates the results of Northern blotting analysis of genes expressed in response to a shear stress stimulus, showing their changes of expression with time. Lanes 18-28 show shear stress-dependent increases of expression for A4RS-604, -626, -916, -002, -049, -230, -239, -242, -491, -578 and -829, respectively. In each blot, 4 µg of total RNA samples derived from HUVEC having shear stress application times of 0, 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 20 hours respectively were electrophoresed as viewed from left to right.

FIG. 5 illustrates the construction of the plasmid pAMo-002 for the expression in animal cells.

FIG. 6A and FIG. 6B are diagrams showing the apoptosis suppressing activity of A4RS-041. FIG. 6A shows changes with time when the anti-Fas monoclonal antibody concentration was fixed at 100 ng/ml, and FIG. 6B shows dependence on the anti-Fas monoclonal antibody concentration when the stimulation time was fixed at 36 hours.

● represents HeLa cells into which A4RS-041 was introduced, and ■ represents HeLa cells into which GFP was introduced.

FIG. 7A and FIG. 7B are diagrams showing the distribution of expression of A4RS-041. FIG. 7A is a diagram showing the results obtained by analyzing the expression of A4RS-041 in human normal tissues by Northern blotting. FIG. 7B is a diagram showing the results obtained by analyzing the expression of A4RS-041 and LFG in human vascular endothelial cells and human brain by RT-PCR.

FIG. 8 is a diagram showing the amino acid sequence homology of A4RS-041 and LFG.

Detailed Description of the Invention

[0018] The present invention will be more specifically described hereinbelow. No particular limitation is placed on the type of cells used to prepare the DNA of the present invention, so long as they exhibit responsiveness to the application of a shear stress. However, adhesion type cells are preferred. Examples thereof include vascular endothelial cells, and human vascular endothelial cells are especially preferred. More preferred are human umbilical vein endothelial cells (HUVECs). These vascular endothelial cells can be easily separated from a human umbilical cord according to the method described in Cell (in Japanese), 20, 329(1988) or Human Cell, 1, 188(1988). It is also possible to obtain and use secondary cultured cells having been separated. The passage number of vascular endothelial cells is not critical, provided that they retain properties as vascular endothelial cells. However, vascular endothelial cells having a passage number of 20 or less are preferred.

[0019] The culture medium used for cell culture may have a conventionally known composition. In the case, for example, of vascular endothelial cells, it is preferable to use a cell culture medium to which 0 to 20% of the blood serum of an animal such as cattle is added. More preferred is E-GM medium (containing 2% fetal calf serum; manufactured by Kurabo Industries, Ltd.) or M199 medium having 20% fetal calf serum added thereto. In order to promote the growth of cells, a cell growth factor such as ECGS (endothelial cell growth supplement), EGF (epidermal growth factor) or

basic FGF (fibroblast growth factor) may be added to the culture medium. A high shear stress can be applied to the cultured cells by adding dextran or the like to the culture medium and thereby increasing the viscosity of the culture medium.

[0020] As the culture apparatus permitting the application of a shear stress, there may be used an apparatus of the micro-carrier type [Am. J. Physiol., 259, H804(1990)], the rotary disc type [Biorheology, 25, 461(1988)], the parallel plate type [Biotechnol. Bioeng., 27, 1021(1985)] or the like.

[0021] In the application of a shear stress, no particular limitation is placed on the method for the culture of vascular endothelial cells. One exemplary method is as follows. Vascular endothelial cells are allowed to adhere to micro-carriers and suspended in a culture medium within a spinner flask. Although the incubation temperature may be any desired temperature that permit the culture of the cells, it is preferable to use a temperature of 37°C. The incubation is preferably carried out in an incubator filled with 5% carbon dioxide gas. No particular limitation is placed on the number of cells harvested, so long as RNA can be extracted therefrom. A typical example thereof is a number of that order which can be obtained by ordinary culture techniques, and a number of not less than 1×10^6 cells is preferred. Although the incubation time is not specified, it is preferable to use an incubation time at which the expression of a gene is distinctly changed as compared with a culture without the application of a shear stress. Especially preferred is an incubation time which provides good viability of the cells. Specifically, an incubation time in the range of 4 to 24 hours is useful.

[0022] As the method for preparing total RNA from vascular endothelial cells having a shear stress applied thereto, the guanidine thiocyanate-caesium trifluoroacetate method [Methods in Enzymol., 154, 3(1987)] or the like may be employed.

[0023] As the method for preparing poly(A)⁺ RNA from total RNA, the oligo(dT)-immobilized cellulose column method (Molecular Cloning, Second Edition) or the like may be employed.

[0024] Furthermore, mRNA may be prepared by using a kit such as Fast Track mRNA Isolation Kit (manufactured by Invitrogen) or Quick Prep mRNA Purification Kit (manufactured by Amersham Pharmacia Biotech).

[0025] Now, the method for the construction of a cDNA library is described below. Usable methods for the construction of a cDNA library include the methods described in Molecular Cloning, Second Edition, Current Protocols in Molecular Biology, DNA Cloning 1: Core Techniques, A Practical Approach, Second Edition, Oxford University Press (1995), and the like; and methods using a commercially available kit such as Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning (manufactured by Life Technologies) or ZAP-cDNA Synthesis Kit (manufactured by Stratagene).

[0026] As a cloning vector for the construction of a cDNA library, there may be used any of phage vectors, plasmid vectors and the like, provided that they can replicate autonomously in *Escherichia coli* K12 strain. Specific examples thereof include ZAP Express [manufactured by Stratagene; Strategies, 5, 58(1992)], pBluescript II SK(+) [Nucleic Acids Res., 17, 9494(1989)], λ zap II (manufactured by Stratagene), λ gt10, λ gt11 [DNA Cloning, A Practical Approach, 1, 49(1985)], λ BlueMid (manufactured by Clontech), λ ExCell (manufactured by Amersham Pharmacia Biotech), pT7T318U (manufactured by Amersham Pharmacia Biotech), pcD2 [Mol. Cell. Biol., 3, 280(1983)] and pUC18 [Gene, 33, 103(1985)].

[0027] As a *Escherichia coli* for introducing vectors having cDNAs integrated therein, there may be used any microorganism that belongs to *Escherichia coli*. Specifically, *Escherichia coli* XL1-Blue MRF' [manufactured by Stratagene; Strategies, 5, 81(1992)], *Escherichia coli* C600 [Genetics, 39, 440(1954)], *Escherichia coli* Y1088 [Science, 222, 778(1983)], *Escherichia coli* Y1090 [Science, 222, 778(1983)], *Escherichia coli* NM522 [J. Mol. Biol., 166, 1(1983)], *Escherichia coli* K802 [J. Mol. Biol., 16, 118(1966)], *Escherichia coli* JM105 [Gene, 38, 275(1985)] and the like may be used.

[0028] Since this cDNA library has the characteristics of vascular endothelial cells having a shear stress applied thereto, it is useful, for example, in cloning a gene associated with a lesion occurring in vital vascular regions undergoing a change of shear stress (specifically, the formation of arteriosclerotic lesions, or the like) and in developing pharmaceuticals by controlling the expression of the gene. Moreover, this cDNA library is different in the types and quantities of genes contained therein, from a cDNA library constructed by using mRNA derived from another type of cells (specifically, standing-cultured vascular endothelial cells having no shear stress applied thereto) as a template. Accordingly, it is possible to isolate the above-described gene associated with the formation of arteriosclerotic lesions or a protein encoded by the gene while using the difference as an index.

[0029] As the method for concentrating genes exhibiting an increase of expression by the application of a shear stress from the cDNA library so constructed, there may be employed a method such as the subtraction method [Proc. Natl. Acad. Sci. USA, 88, 2825(1991)] or differential hybridization [J. Biol. Chem., 265, 2973(1990)].

[0030] As the method for selecting clones having expression specificity (i.e., exhibiting an increase of expression by the application of a shear stress) from the subtraction library in which such genes are concentrated in the above-described manner, there may be employed Northern hybridization [Molecular Cloning, Second Edition], RT(reverse-transcribed)-PCR [Current Protocols in Molecular Biology] or the like.

[0031] With respect to the shear stress-responsive clone selected in the above-described manner, the nucleotide sequence of the DNA can be determined by analyzing it according to a commonly employed nucleotide sequence

analysis method such as the dideoxy method of Sanger et al. [Proc. Natl. Acad. Sci. USA, 74, 5463(1977)], or by means of a nucleotide sequence analyzer such as 373A DNA Sequencer (manufactured by Perkin Elmer).

[0032] The novelty of the nucleotide sequence determined in the above-described manner can be confirmed by using a homology search program (e.g., blast) to search the nucleotide sequence in nucleotide sequence databases such as GenBank, EMBL and DDBJ, and thereby ascertaining that the databases do not include any nucleotide sequence having a distinct identity to the aforesaid nucleotide sequence and hence considered to be identical thereto.

[0033] When the DNA obtained in the above-described manner is a partial DNA of the cDNA corresponding to a shear stress-related mRNA, a clone containing the full-length cDNA may be selected again from the cDNA library by using the DNA obtained in the above-described manner as a probe.

[0034] The selection of a cDNA clone from the cDNA library may be carried out by colony hybridization or plaque hybridization using a probe labeled with an isotope or digoxigenin [Sambrook et al., Molecular Cloning, Second Edition (1989)].

[0035] Examples of the full-length cDNA of the shear stress-responsive gene having a novel nucleotide sequence, which is obtained in the above-described manner, include DNAs having the nucleotide sequences represented by SEQ ID NO:143, 145, 147, 149, 151, 153, 155, 157, 168, 170 and 172.

[0036] Once the full-length cDNA of a shear stress-related gene is obtained and its nucleotide sequence is determined as described above, the desired DNA can be obtained by preparing primers based on the nucleotide sequence and carrying out PCR [PCR Protocols, Academic Press (1990)] while using cDNA synthesized from mRNA or a cDNA library as a template. Moreover, the desired DNA may also be prepared by using a DNA synthesizer to synthesize it chemically on the basis of the determined nucleotide sequence of the DNA. Usable DNA synthesizers include Model 392 DNA Synthesizer (manufactured by Perkin Elmer) using the phosphoramidite method, and the like.

[0037] On the basis of the nucleotide sequence information of the aforesaid DNA and DNA fragment, an oligonucleotide and an antisense oligonucleotide each having a partial sequence of the DNA of the present invention may be prepared according to a conventional method or by means of a DNA synthesizer.

[0038] Examples of the oligonucleotide or antisense oligonucleotide include a sense primer corresponding to a nucleotide sequence on the 5'-terminal side and an antisense primer corresponding to a nucleotide sequence on the 3'-terminal side, both in a partial nucleotide sequence of mRNA to be detected. However, the base corresponding to uracil in mRNA is thymidine in oligonucleotide primers. Preferably, the sense primer and antisense primer are oligonucleotides whose melting temperatures (T_m) and numbers of bases are not extremely different from each other and which consist of 10 to 40 bases.

[0039] Moreover, in the present invention, there may be used derivatives of the nucleotides. Examples thereof include methyl derivatives and phosphothioate derivatives of the nucleotides.

[0040] Now, the method for the preparation of a protein having an activity involved in the formation of an arteriosclerotic lesion is described below.

[0041] The cDNA of the shear stress-responsive gene, which was obtained in the above-described manner, encodes a protein having an activity involved in the formation of an arteriosclerotic lesion.

[0042] The activity involved in the formation of an arteriosclerotic lesion means an activity regulating the development of arteriosclerosis, and preferably an activity preventing the development of arteriosclerosis. Examples thereof include, but are not limited to, the following activities.

[0043] They include regulation of the incorporation of low-density lipoprotein (LDL) into the vascular endothelium; regulation of the incorporation of oxidized LDL into the vascular endothelium; regulation of the expression of LDL receptors in vascular endothelial cells; regulation of the production of oxidized LDL in vascular endothelial cells; regulation of the expression of scavenger receptors in the vascular endothelium; regulation of the infiltration of lymphocytes into blood vessels; regulation of the expression of a cell surface adhesion molecule promoting the infiltration of lymphocytes into blood vessels in vascular endothelial cells; regulation of the proliferation of vascular smooth muscle produced in vascular endothelial cells; regulation of the apoptosis of vascular endothelial cells; and the like.

[0044] The DNAs and proteins of the present invention have been found on the basis of their shear stress-dependent increase of expression in vascular endothelial cells. As described in the Background of the Invention, it is generally known that arteriosclerosis occurs frequently in places where a low shear stress is produced and the separation or stagnation of a flow or turbulence (e.g., eddies) tends to occur. Accordingly, the DNAs and proteins of the present invention are especially useful for the treatment or prevention of arteriosclerosis or various vascular diseases caused thereby, including non-limitative examples such as cardiac insufficiency, restenosis after PTCA, and hypertension.

[0045] If necessary, a DNA fragment of appropriate length containing a portion encoding the protein is prepared on the basis of the full-length cDNA.

[0046] An expression plasmid for the protein is created by inserting the DNA fragment or the full-length cDNA into an expression vector on the downstream side of a promoter.

[0047] The expression plasmid is introduced into a host cell suited to the expression vector.

[0048] As the host cell, there may be used any host cell that enables the expression of the desired DNA. For example,

there may be used bacteria belonging to the genera Escherichia, Serratia, Corynebacterium, Brevibacterium, Pseudomonas, Bacillus and Microbacterium; yeasts belonging to the genera Kluyveromyces, Saccharomyces, Shizosaccharomyces, Trichosporon and Schwanniomycetes; animal cells; and insect cells.

[0049] As the expression vector, there is used a vector which can be autonomously replicated or incorporated into a chromosome in the aforesaid host cell and which contains a promoter at a position capable of transcribing the shear stress-responsive DNA.

[0050] When a bacterium or the like is used as the host cell, the shear stress-responsive DNA expression vector is preferably a recombinant vector which can be autonomously replicated in the bacterium and which consists of a promoter, a ribosome-binding sequence, the shear stress-responsive DNA and a transcription termination sequence. A gene controlling the promoter may be contained therein.

[0051] Examples of such expression vectors include pBTrp2, pBTac1, pBTac2 (all commercially available from Boehringer Mannheim), pKK233-2 (manufactured by Amersham Pharmacia Biotech), pSE280 (manufactured by Invitrogen), pGEMEX-1 (manufactured by Promega), pQE-8 (manufactured by QIAGEN), pKYP10 (Japanese Published Unexamined Patent application No. 110600/83), pKYP200 [Agricultural Biological Chemistry, 48, 669 (1984)], pLSA1 [Agric. Biol. Chem., 53, 277(1989)], pGEL1 [Proc. Natl. Acad. Sci. USA, 82, 4306(1985)], pBluescript II SK(-) (manufactured by Stratagene), pGEX (manufactured by Amersham Pharmacia Biotech), pET-3 (manufactured by Novagen), pTerm2 (USP 4686191, USP 4939094, USP 5160735), pSupex, pUB110, pTP5, pC194, pEG400 [J. Bacteriol., 172, 2392(1990)].

[0052] The promoter may be any promoter that can express a gene in the host cell. Examples thereof include promoters derived from Escherichia coli and phages, such as trp promoter (Ptrp), lac promoter (Plac), P_L promoter, P_R promoter and T7 promoter; and SP01 promoter, SP02 promoter and penP promoter. Moreover, there may also be used artificially designed or modified promoters and the like, such as a promoter comprising two Ptrp's connected in series (Ptrpx2), tac promoter, letI promoter [Gene, 44, 29(1986)] and lacT7 promoter.

[0053] The ribosome-binding sequence may be any ribosome-binding sequence that can be expressed in the host cell. However, it is preferable to use a plasmid in which the distance between the Shine-Dargarno sequence and the initiation codon is adjusted to a suitable length (e.g., 6-18 bases).

[0054] In the nucleotide sequence of the protein-encoding part of the shear stress-responsive DNA of the present invention, some residues may be replaced so as to give the codons most suitable for its expression in the host. Thus, the production rate of the desired protein can be improved.

[0055] A transcription termination sequence is not necessarily required for the expression of the shear stress-responsive DNA of the present invention. However, it is desirable to dispose a transcription termination sequence just downstream of the structural gene.

[0056] Examples of the host cell include microorganisms belonging to the genera Escherichia, Serratia, Corynebacterium, Brevibacterium, Pseudomonas, Bacillus and the like, such as Escherichia coli XL1-Blue, Escherichia coli XL2-Blue, Escherichia coli DH1, Escherichia coli MC1000, Escherichia coli KY3276, Escherichia coli W1485, Escherichia coli JM109, Escherichia coli HB101, Escherichia coli No.49, Escherichia coli W3110, Escherichia coli NY49, Bacillus subtilis, Bacillus amyloliquefaciens, Brevibacterium ammoniagenes, Brevibacterium immariophilum ATCC14068, Brevibacterium saccharolyticum ATCC14066, Corynebacterium glutamicum ATCC13032, Corynebacterium glutamicum ATCC14067, Corynebacterium glutamicum ATCC13869, Corynebacterium acetoacidophilum ATCC13870, Microbacterium ammoniaphilum ATCC15354, and Pseudomonas sp. D-0110.

[0057] As the method for introducing the recombinant vector, there may be employed any method that can introduce DNA into the aforesaid host cell. Examples thereof include the calcium ion method [Proc. Natl. Acad. Sci. USA, 69, 2110(1972)], the protoplast method (Japanese Published Unexamined Patent Application No. 248397/88), and the methods described in Gene, 17, 107(1982) and Molecular & General Genetics, 168, 111(1979).

[0058] Where a yeast is used as the host cell, usable expression vectors include, for example, YEp13 (ATCC37115), YEp24 (ATCC37051), YCp50 (ATCC37419), pHS19 and pHS15.

[0059] The promoter may be any promoter that can express a gene in the yeast. Examples thereof include PHO5 promoter, PGK promoter, GAP promoter, ADH promoter, gal 1 promoter, gal 10 promoter, heat shock protein promoter, MFα1 promoter and CUP 1 promoter.

[0060] Examples of the host cell include Saccharomyces cerevisiae, Shizosaccharomyces pombe, Kluyveromyces lactis, Trichosporon pullulans and Schwanniomyces alluvius.

[0061] As the method for introducing the recombinant vector, there may be employed any method that can introduce DNA into yeasts. Examples thereof include the electroporation method [Methods. Enzymol., 194, 182(1990)], the spheroplast method [Proc. Natl. Acad. Sci. USA, 75, 1929(1978)], the lithium acetate method [J. Bacteriol., 153, 163(1983)], and the methods described in Proc. Natl. Acad. Sci. USA, 75, 1929(1978).

[0062] Where an animal cell is used as the host cell, usable expression vectors include, for example, pcDNA1, pcDM8 (manufactured by Funakoshi), pAGE107 [Japanese Published Unexamined Patent Application No. 22979/90; Cytotechnology, 3, 133(1990)], pAS3-3 (Japanese Published Unexamined Patent Application No. 227075/90), pCDM8 [Na-

ture, 329, 840(1987)], pcDNA/Amp (manufactured by Invitrogen), pREP4 (manufactured by Invitrogen), pAGE103 [J. Biochem., 101, 1307(1987)] and pAGE210.

[0063] The promoter may be any promoter that can be expressed in the animal cell. Examples thereof include the promoter of the IE (immediate early) gene of cytomegalovirus (human CMV), the early promoter of SV40, the promoter of retroviruses, metallothionein promoter, heat shock protein promoter, and SR α promoter. The enhancer of the IE gene of human CMV may be used in conjunction with the promoter.

[0064] Examples of the host cell include Namalwa cell derived from a human, COS cell derived from a monkey, CHO cell derived from a Chinese hamster, and HBT5637 (Japanese Published Unexamined Patent Application No. 299/88).

[0065] As the method for introducing the recombinant vector into the animal cell, there may be employed any method that can introduce DNA into animal cells. Examples thereof include the electroporation method [Cytotechnology, 3, 133(1990)], the calcium phosphate method (Japanese Published Unexamined Patent Application No. 227075/90), the lipofection method [Proc. Natl. Acad. Sci. USA, 84, 7413(1987)], and the methods described in Virology, 52, 456(1973). Transformants may be harvested and cultured according to the method described in Japanese Published Unexamined Patent Application No. 227075/90 or 257891/90.

[0066] Where an insect cell is used as the host, the protein may be expressed according to the method described, for example, in Baculovirus Expression Vectors, A Laboratory Manual, Current Protocols in Molecular Biology Supplement 1-38 (1987-1997), or Bio/Technology, 6, 47(1988).

[0067] Specifically, a recombinant gene transfer vector and a baculovirus are co-introduced into an insect cell. After a recombinant virus is obtained in the culture supernatant of the insect cell, an insect cell is further infected with the recombinant virus to express the protein.

[0068] Examples of the gene transfer vector used in this method include pVL1392, pVL1393 and pBlueBac11 (all manufactured by Invitrogen).

[0069] As the baculovirus, there may be used, for example, autographa californica nuclear polyhedrosis virus that is a virus infecting insects belonging to Noctuidae.

[0070] As the insect cell, there may be used Sf9 and Sf21 that are ovarian cells of *Spodoptera frugiperda* [Baculovirus Expression Vectors, A Laboratory Manual, W.H. Freeman and Company, New York (1992)], High 5 that is an ovarian cell of *Trichoplusia ni* (manufactured by Invitrogen), and the like.

[0071] The methods which may be employed for co-introducing the aforesaid recombinant gene transfer vector and the aforesaid baculovirus into an insect cell in order to prepare a recombinant virus include, for example, the calcium phosphate method (Japanese Published Unexamined Patent Application No. 227075/90) and the lipofection method [Proc. Natl. Acad. Sci. USA, 84, 7413(1987)].

[0072] The expression of the gene may be effected not only by direct expression, but also by secretory production, fusion protein expression or the like, for example, according to the methods described in Molecular Cloning, Second Edition.

[0073] When the gene is expressed by means of a yeast, an animal cell or an insect cell, the protein having a sugar or sugar chain added thereto may be obtained.

[0074] A shear stress-responsive protein may be prepared by culturing a transformant containing a recombinant DNA having the shear stress-responsive DNA integrated thereinto in a culture, causing a shear stress-responsive protein to be produced and accumulated in the culture, and harvesting the protein from the resulting culture.

[0075] In order to culture the transformant of the present invention for the preparation of the shear stress-responsive protein in a culture medium, there may be employed a common method for the culture of the host.

[0076] When the transformant of the present invention is a procaryote (e.g., *Escherichia coli*) or a eucaryote (e.g., yeast), the culture medium for the culture of such microorganisms may be a natural medium or a synthetic medium, provided that this medium contains a carbon source, a nitrogen source, minerals and other nutrients which can be assimilated by the microorganism and that this medium permits the transformant to be efficiently cultured.

[0077] The carbon source may be any carbon source that can be assimilated by the respective microorganisms. There may be used carbohydrates such as glucose, fructose, sucrose, molasses containing them, starch and starch hydrolyzate; organic acids such as acetic acid and propionic acid; and alcohols such as ethanol and propanol.

[0078] As the nitrogen source, there may be used ammonia; ammonium salts of various inorganic acids or organic acids, such as ammonium chloride, ammonium sulfate, ammonium acetate and ammonium phosphate; and other nitrogen-containing compounds, as well as peptone, meat extract, yeast extract, corn steep liquor, casein hydrolyzate, soybean meal and soybean meal hydrolyzate, various fermented bacterial cells and their digestion products, and the like.

[0079] As the minerals, there may be used potassium dihydrogen phosphate, dipotassium hydrogen phosphate, magnesium phosphate, magnesium sulfate, sodium chloride, ferrous sulfate, manganese sulfate, copper sulfate, calcium carbonate and the like.

[0080] The cultivation is carried out under aerobic conditions, for example, according to a shaking culture or deep aerated spinner culture technique. The incubation temperature should be in the range of 15 to 40°C and the incubation

time usually ranges from 16 hours to 7 days. During cultivation, pH is maintained at 3.0 to 9.0. The adjustment of pH is made with an inorganic or organic acid, an alkaline solution, urea, calcium carbonate, ammonia or the like.

[0081] During cultivation, an antibiotic such as ampicillin or tetracycline may be added to the culture medium, if necessary.

5 [0082] When a microorganism transformed with an expression vector using an inducible promoter is cultured, an inducer may be added to the culture medium, if necessary. For example, when a microorganism transformed with an expression vector using *lac* promoter is cultured, isopropyl- β -D-thiogalactopyranoside (IPTG) or the like may be added to the culture medium, and when a microorganism transformed with an expression vector using *trp* promoter is cultured, indoleacrylic acid (IAA) or the like may be added to the culture medium.

10 [0083] As the culture medium for culturing a transformant obtained by using an animal cell as the host cell, there may be used any of commonly used culture media such as RPMI1640 medium [The Journal of the American Medical Association, 199, 519(1967)], Eagle's MEM [Science, 122, 501(1952)], Dulbecco-modified MEM [Virology, 8, 396 (1959)], 199 medium [Proceeding of the Society for the Biological Medicine, 73, 1(1950)], and culture media prepared by adding fetal calf serum or the like to the foregoing media.

15 [0084] The cultivation is usually carried out for 1 to 7 days under conditions including a pH of 6 to 8, a temperature of 30 to 40°C, and the presence of 5% CO₂.

[0085] During cultivation, an antibiotic such as kanamycin or penicillin may be added to the culture medium, if necessary.

20 [0086] As the culture medium for culturing a transformant obtained by using an insect cell as the host cell, there may be used any of commonly used culture media such as TNM-FH medium (manufactured by Pharmingen), Sf-900 II SFM medium (manufactured by Life Technologies), ExCel1400, ExCel1405 (both manufactured by JRH Biosciences), and Grace's Insect Medium [Nature, 195, 788(1962)].

[0087] The cultivation is usually carried out for 1 to 5 days under conditions including a pH of 6 to 7 and a temperature of 25 to 30°C.

25 [0088] During cultivation, an antibiotic such as gentamicin may be added to the culture medium, if necessary.

[0089] In order to isolate and purify a protein having an activity associated with arteriosclerosis in accordance with the present invention, from the culture of the transformant of the present invention, there may be employed common techniques for the isolation and purification of enzymes.

30 [0090] For example, where the protein of the present invention is expressed in a dissolved state within cells, the cells are collected by centrifugation after completion of the incubation, suspended in an aqueous buffer, and disrupted with a sonicator, French press, Manton Gaulin homogenizer, Dynomill or the like to obtain a cell-free extract. From the supernatant obtained by centrifuging the cell-free extract, a purified preparation may be obtained by employing common techniques for the isolation and purification of enzymes, either alone or in combination. These techniques include, for example, solvent extraction, salting-out with ammonium sulfate or the like, desalting, precipitation with an organic solvent, anion-exchange chromatography using a resin such as diethylaminoethyl (DEAE)-Sephacrose or DIAION HPA-75 (manufactured by Mitsubishi Chemical Corp.), cation-exchange chromatography using a resin such as S-Sephacrose FF (manufactured by Amersham Pharmacia Biotech), hydrophobic chromatography using a resin such as butyl Sepharose or phenyl Sepharose, gel filtration with a molecular sieve, affinity chromatography, chromatofocusing, and electrophoresis such as isoelectric focusing.

40 [0091] Where the protein is expressed in the form of an insoluble material within cells, the cells are collected, disrupted and centrifuged. Thus, the insoluble protein is recovered as a precipitate fraction.

[0092] The insoluble protein so recovered is solubilized with a protein denaturing agent.

45 [0093] The solubilized solution is diluted or dialyzed to reduce the concentration of the protein denaturing agent in the solubilized solution and thereby refold the protein to a normal stereostructure. Thereafter, a purified preparation of the protein may be obtained according to the same isolation and purification techniques as described above.

[0094] Where the protein of the present invention or a derivative thereof (e.g., a glycosylated product) is secreted out of cells, the protein or a derivative thereof (e.g., a glycosylated product) may be recovered from the culture supernatant. Specifically, the culture supernatant is recovered from the resulting culture according to a technique such as centrifugation. Then, a purified preparation may be obtained from the culture supernatant by employing the same isolation and purification techniques as described above.

50 [0095] Examples of the protein thus obtained include proteins having the amino acid sequences represented by SEQ ID NO:144, 146, 148, 150, 152, 154, 156, 158, 169, 171, 173 and the like.

[0096] The protein expressed in the above-described manner may also be prepared by chemical synthesis processes such as Fmoc method (fluorenylmethyloxycarbonyl method) and tBoc method (t-butyloxycarbonyl method). Alternatively, they may also be synthesized by means of a peptide synthesizer manufactured by Sowa Trading Co. (Advanced ChemTech, USA), Perkin Elmer, Amersham Pharmacia Biotech, Aloka (Protein Technology Instrument, USA), Kurabo (Synthecell-Vega, USA), PerSeptive Japan, Ltd. (PerSeptive, USA), Shimadzu Corporation or the like.

[0097] Now, the methods for the preparation of antibodies recognizing the protein of the present invention are de-

scribed below.

(i) Preparation of a polyclonal antibody

5 [0098] A purified full-length or partial fragment of the protein obtained in the above-described manner, or a peptide having a partial amino acid sequence of the protein of the present invention is used as an antigen. A polyclonal antibody may be prepared by administering this antigen to an animal.

[0099] As the animal to which the antigen is administered, there may be used a rabbit, goat, mouse, hamster or the like. The dose of the antigen is preferably in the range of 50 to 100 μ g per animal. When a peptide is used, it desirably
10 used after being covalently bonded to carrier protein such as keyhole limpet haemocyanin or bovine thyroglobulin. The peptide used as an antigen may be synthesized by means of a peptide synthesizer.

[0100] After the first administration, the antigen is administered 3 to 10 times at intervals of 1 to 2 weeks. After each administration, blood is collected from the venous plexus of fundus oculi on the 3rd to 7th day, and the reaction of the serum with the antigen used for immunization is confirmed by enzyme immunoassay [Enzyme-Linked Immunosorbent
15 assay (ELISA) (In Japanese), Igaku Shoin, 1976; Antibodies-A Laboratory Manual, Cold Spring Harbor Laboratory (1988)] or the like.

[0101] Serum is obtained from a nonhuman mammal whose serum exhibits a sufficient antibody titer against the antigen used for immunization. Then, a polyclonal antibody can be obtained by separating and purifying the serum.

[0102] The techniques which can be employed for the purpose of separation and purification include centrifugation; salting-out with 40-50% saturated ammonium sulfate, caprylic acid precipitation [Antibodies, A Laboratory Manual,
20 Cold Spring Harbor Laboratory (1988)], chromatography using a DEAE-Sepharose column, anion-exchange column, protein A or G column, or gel filtration column, and the like. These techniques may be used either alone or in combination.

25 (ii) Preparation of a monoclonal antibody

(a) Preparation of antibody-producing cells

[0103] A rat whose serum exhibits a sufficient antibody titer against the partial fragment polypeptide of the protein of the present invention used for immunization is used as a source of antibody-producing cells.
30

[0104] After the antigenic substance is finally administered to the rat exhibiting the aforesaid antibody titer, the spleen is excised on the 3rd to 7th day. The spleen is minced in MEM (manufactured by Nissui Seiyaku Co., Ltd.) and loosened with a pincette. After this suspension is centrifuged at 1,200 rpm for 5 minutes, the supernatant is discarded. The spleen cells in the resulting precipitate fraction are treated with a Tris-ammonium chloride buffer (pH 7.65) for 1-2
35 minutes to remove erythrocytes, and washed three times with MEM. The spleen cells thus obtained are used as antibody-producing cells.

(b) Preparation of myeloma cells

40 [0105] As the myeloma cells, an established cell line obtained from a mouse or rat is used.

[0106] Usable cell lines include, for example, the 8-azaguanine-resistant mouse (BALB/c-derived) myeloma cell line P3-X63Ag8-U1 (hereinafter abbreviated as P3-U1) [Curr. Topics. Microbiol. Immunol., 81, 1(1978); Europ. J. Immunol., 6, 511(1976)], SP2/0-Ag14(SP-2) [Nature, 276, 269(1978)], P3-X63-Ag8653(653) [J. Immunol., 123, 1548(1979)], and P3-X63-Ag8(X63) [Nature, 256, 495(1975)].

[0107] Such a cell line is subcultured in 8-azaguanine medium [a culture medium prepared by adding glutamine (1.5 mmol/l), 2-mercaptoethanol (5×10^{-5} M), gentamicin (10 μ g/ml) and fetal calf serum (FCS) (manufactured by CSL, 10%) to RPMI-1640 medium (the resulting medium is hereinafter referred to as the normal medium) and further adding 8-azaguanine (15 μ g/ml) thereto]. Three or four days before cell fusion, the cell line is cultured in the normal medium, and not less than 2×10^7 cells are used for the purpose of cell fusion.
50

(c) Formation of hybridomas

[0108] The antibody-producing cells obtained in (a) and the myeloma cells obtained in (b) are thoroughly washed with MEM or PBS (1.83 g disodium phosphate, 0.21 g monopotassium phosphate, 7.65 g sodium chloride, 1 liter distilled water, pH 7.2), and mixed so that the antibody-producing cells and the myeloma cells are present in a ratio of 5-10:1. After this mixture was centrifuged at 1,200 rpm for 5 minutes, the supernatant is discarded.
55

[0109] The mass of cells in the resulting precipitate fraction is thoroughly loosened, and 0.2 to 1 ml (per 10^8 antibody-producing cells) of a solution prepared by mixing 2 g of polyethylene glycol-1000 (PEG 1000), 2 ml of MEM, and 0.7

ml of dimethyl sulfoxide (DMSO) is added to the mass of cells at 37°C with stirring. Moreover, 1 to 2 ml of MEM is added thereto several times at intervals of 1 to 2 minutes. After completion of the addition, MEM is added to make a total volume of 50 ml.

[0110] After the suspension so prepared is centrifuged at 900 rpm for 5 minutes, the supernatant is discarded. The cells of the resulting precipitate fraction are gently loosened, and gently suspended in 100 ml of HAT medium [a culture medium prepared by adding hypoxanthine (10^{-4} M), thymidine (1.5×10^{-5} M) and aminopterin (4×10^{-7} M) to the normal medium] by repeated sucking and blowing with a measuring pipette.

[0111] This suspension is pipetted into the wells of a 96-well culture plate in an amount of 100 μ l per well, and incubated at 37°C in a 5% CO₂ incubator for 7 to 14 days. After incubation, a portion of the culture supernatant is taken, and hybridomas reacting specifically with the partial fragment polypeptide of the protein of the present invention are selected according to enzyme immunoassay as described in Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Chapter 14 (1988) or the like.

[0112] An exemplary procedure for enzyme immunoassay is described below.

[0113] The partial fragment polypeptide of the protein of the present invention, which was used as an antigen at the time of immunization, is coated on a suitable plate and reacted with a first antibody comprising the culture supernatant of a hybridoma or the purified antibody obtained in (d) below, further reacted with a second antibody comprising an anti-rat or anti-mouse immunoglobulin antibody labeled with biotin, an enzyme, a chemiluminescent substance, a radioactive compound or the like, and then subjected to a reaction depending on the labeling material. Thus, the hybridomas reacting specifically with the protein of the present invention are selected as hybridomas for producing a monoclonal antibody against the protein of the present invention.

[0114] Using these hybridomas, cloning is repeated twice according to the limiting dilution method [HT medium (HAT medium freed of aminopterin) was used for the first time and the normal medium for the second time]. A hybridoma exhibiting a high antibody titer stably is selected as a hybridoma strain capable of producing an antibody against the polypeptide of the protein of the present invention.

(d) Preparation of a monoclonal antibody

[0115] 5×10^6 to 20×10^6 cells per animal of the hybridoma capable of producing a monoclonal antibody against the protein of the present invention, which was obtained in (c), is intraperitoneally injected into 8- to 10-weeks-old mice or nude mice having been subjected to a pristane treatment (i.e., having been treated by administering 0.5 ml of 2,6,10,14-tetramethylpentadecane (pristane) intraperitoneally and kept for 2 weeks). After 10 to 21 days, the hybridoma develops into an ascites tumor. Ascites is collected from a mouse having developed an ascites tumor, and centrifuged at 3,000 rpm for 5 minutes to remove any solid matter. From the resulting supernatant, a monoclonal antibody may be purified and harvested in the same manner as described above in connection with a polyclonal antibody.

[0116] The subclass of the antibody may be determined by means of a mouse monoclonal antibody typing kit or a rat monoclonal antibody typing kit. The amount of protein may be determined by the Lowry method or calculated from the absorbance at 280 nm.

[0117] Now, the method for preparing a recombinant virus vector useful for producing the protein of the present invention in a specific human tissue is described below.

[0118] The cDNA of the shear stress-responsive gene, which was obtained in the above-described manner, encodes a protein having an activity involved in the formation of an arteriosclerotic lesion.

[0119] If necessary, a DNA fragment of appropriate length containing a portion encoding the protein is prepared from the full-length cDNA.

[0120] A recombinant virus vector is created by inserting the DNA fragment or the full-length cDNA into a virus vector on the downstream side of a promoter.

[0121] This recombinant virus vector is introduced into a packaging cell suited to the vector.

[0122] As the packaging cell, there may be used any cell that, when the recombinant virus vector lacks any of the genes encoding proteins necessary for the packaging of the virus, can supply the deficient proteins. For example, there may be used human kidney-derived HEK293 cell or mouse fibroblast cell NIH3T3. The proteins supplied by the packaging cell include mouse retrovirus-derived proteins such as gag, pol and env for a retrovirus vector; HIV virus-derived proteins such as gag, pol, env, vpr, vpu, vif, tat, rev and nef for a lentivirus vector; adenovirus-derived proteins such as E1A and E1B for an adenovirus vector; and proteins such as Rep(p5, p19, p40) and Vp(Cap) for an adeno-associated virus.

[0123] As the virus vector, there is used a virus vector which can produce the recombinant virus in the aforesaid packaging cell and which contains a promoter at a position permitting the shear stress-responsive DNA to be transcribed in a target cell. As the plasmid vector, there may be used MFG [Proc. Natl. Acad. Sci. USA, 92, 6733-6737 (1995)], pBabePuro [Nucleic Acids Res., 18, 3587-3596(1990)], LL-CG, CL-CG, CS-CG, CLG [Journal of Virology, 72, 8150-8157(1998)] and pAdexl [Nucleic Acids Res., 23, 3816-3821(1995)]. The promoter may be any promoter that

can be expressed in human tissues. Examples thereof include the promoter of the IE (immediate early) gene of cytomegalovirus (human CMV), the early promoter of SV40, the promoter of retroviruses, metallothionein promoter, heat shock protein promoter, and SR α promoter. The enhancer of the IE gene of human CMV may be used in conjunction with the promoter.

[0124] Examples of the method for introducing the aforesaid recombinant virus vector into the aforesaid packaging cell include the calcium phosphate method (Japanese Published Unexamined Patent Application No. 227075/90) and the lipofection method [Proc. Natl. Acad. Sci. USA, 84, 7413(1987)].

[0125] Now, the method for detecting a shear stress-responsive mRNA using the shear stress-responsive DNA of the present invention is described below.

[0126] The DNAs which can be used in this method include, for example, DNAs having the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 116, 117, 119, 121, 123, 125, 127, 129, 130, 131, 132, 133, 134, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 168, 170, 172 and the like. Moreover, they include a DNA having a sequence of part of the foregoing DNA, an oligonucleotide DNA having the nucleotide sequence of 5 to 60 consecutive bases in the foregoing DNA, and preferably an oligonucleotide DNA having the nucleotide sequence of 10 to 40 consecutive bases therein. Furthermore, they include a shear stress-responsive DNA capable of hybridizing with the foregoing DNA or a fragment thereof under stringent conditions.

[0127] The identification of a change in the expression level of a shear stress-responsive mRNA and a structural change of the expressed mRNA in human biological specimens and human primary cultured cells is useful in knowing the risk of developing arteriosclerosis in the future or the cause of an already developed vascular disease.

[0128] Examples of the method for detecting the expression level of a shear stress-responsive mRNA and a structural change thereof include (1) Northern blotting, (2) in situ hybridization, (3) quantitative PCR, (4) differential hybridization, (5) the DNA chip method, and (6) RNase protection assay.

[0129] The materials which can be analyzed by the aforesaid methods include mRNA or total RNA which is obtained from biological specimens (e.g., vascular endothelium, blood serum and saliva) collected from arteriosclerotic patients and healthy subjects, or a primary cultured cell sample prepared by isolating cells from such a biological specimen and culturing them in a suitable culture medium in vitro (the mRNA and total RNA are hereinafter referred to as the specimen-derived RNA). Alternatively, isolated paraffin or cryostat sections of tissues obtained from biological specimens may also be used.

[0130] Northern blotting is a technique in which the specimen-derived RNA is separated by gel electrophoresis, transferred to a support such as a nylon filter, hybridized with a labeled probe prepared from the DNA of the present invention, and then washed to detect a band bound specifically to a shear stress-responsive mRNA. Thus, the expression level of a shear stress-responsive mRNA and a structural change thereof can be detected. The hybridization is carried out by incubating the support under such conditions as a stable hybrid is formed between the probe and a shear stress-responsive mRNA in the specimen-derived RNA. In order to prevent a false positive reaction, it is desirable to carry out the hybridization and washing steps under highly stringent conditions. They are determined according to a large number of factors such as temperature, ionic strength, base composition, probe length and formamide concentration. These factors are described, for example, in Molecular Cloning, Second Edition (as mentioned above).

[0131] The labeled probe used for Northern blotting may be prepared, for example, by incorporating a radioactive isotope, biotin, a fluorescent group, a chemiluminescent group or the like into the DNA of the present invention or an oligonucleotide designed from the sequence of the DNA, according to a well-known technique (nick translation, random priming or kinasing). Since the amount of labeled probe hybridized reflects the expression level of the shear stress-responsive mRNA, the expression level of the shear stress-responsive mRNA can be determined by determining the amount of labeled probe hybridized. Moreover, a structural change of the shear stress-responsive mRNA can be detected by analyzing the binding site of the labeled probe.

[0132] The expression level of a shear stress-responsive mRNA can also be detected by in situ hybridization in which the hybridization and washing steps are carried out by using the aforesaid labeled probe and isolated paraffin or cryostat sections of tissues obtained from the living body. In order to prevent a false positive reaction in in situ hybridization, it is desirable to carry out the hybridization and washing steps under highly stringent conditions. They are determined according to a large number of factors such as temperature, ionic strength, base composition, probe length and formamide concentration. These factors are described, for example, in Current Protocols in Molecular Biology.

[0133] Some methods for detecting a shear stress-responsive mRNA, such as quantitative PCR, differential hybridization, and the DNA chip method, may be carried out on the basis of the synthesis of cDNA by using the specimen-derived RNA, an oligo-dT primer or random primer, and reverse transcriptase (the resulting cDNA is hereinafter referred to as the specimen-derived cDNA). When the specimen-derived RNA is mRNA, both of the aforesaid primers may be used. However, when the specimen-derived RNA is total RNA, it is necessary to use an oligo-dT primer.

[0134] In quantitative PCR, DNA fragments derived from the shear stress-responsive mRNA are amplified by carrying

out PCR while using a template comprising the specimen-derived cDNA and primers designed on the basis of the nucleotide sequence possessed by the DNA of the present invention. Since the amount of the amplified DNA fragments reflects the expression level of the shear stress-responsive mRNA, the amount of the shear stress-responsive mRNA can be determined by using, as an internal control, a DNA encoding actin or G3PDH (glyceraldehyde 3-phosphate dehydrogenase) not responding to a shear stress. Moreover, a structural change of the shear stress-responsive mRNA can be detected by separating the amplified DNA fragments by gel electrophoresis. In this detection method, it is desirable to use suitable primers capable of amplifying a target sequence specifically and efficiently. Such suitable primers can be designed on the basis of the conditions that they do not hybridize between primers or within primers and that they hybridize specifically with the target cDNA at the annealing temperature and separate from the target under denaturing conditions. The quantitative determination of the amplified DNA fragments must be carried out within the range of the number of cycles of PCR in which the amplification product is increasing exponentially. Such a number of cycles of PCR can be known by recovering the amplified DNA fragment produced at each number of cycles of PCR and analyzing it by gel electrophoresis.

[0135] An alteration of the expression level of the shear stress-responsive mRNA can be detected by hybridizing and washing the DNA of the present invention immobilized on a filter or a substrate (e.g., slide glass or silicon) while using a probe comprising the specimen-derived cDNA synthesized from the specimen-derived RNA with the aid of dNTP. The methods based on this principle include methods called differential hybridization [Trends in Genetics, 7, 314-317(1991)] and the DNA chip method [Genome Research, 6, 639-645(1996)]. In both methods, the difference in the expression of the shear stress-responsive mRNA between a control specimen and a target specimen can be accurately detected by immobilizing an internal control (e.g., actin or G3PDH) on the filter or substrate. Moreover, the accurate expression level of the shear stress-responsive mRNA can be determined by synthesizing cDNAs from a control specimen and the specimen-derived RNA using different labeled dNTP and carrying out hybridization with the two labeled cDNA probes simultaneously on one filter or one substrate.

[0136] In RNase protection assay, a promoter sequence (e.g., T7 promoter or SP6 promoter) is first linked to the 3'-terminus of the DNA of the present invention. Then, in an *in vitro* transcription system using RNA polymerase, a labeled antisense RNA is synthesized using labeled rNTP. After this labeled antisense RNA is combined with the specimen-derived RNA to form an RNA-RNA hybrid, it is digested with RNase and a band protected from digestion is detected by gel electrophoresis. The expression level of the shear stress-responsive mRNA can be determined by assaying the protected band.

[0137] Now, the method for detecting a gene causative of arteriosclerosis using the shear stress-responsive DNA of the present invention is described below.

[0138] The DNAs which can be used in this method include, for example, DNAs having the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 116, 117, 119, 121, 123, 125, 127, 129, 130, 131, 132, 133, 134, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 168, 170, 172 and the like. Moreover, they include a DNA having a sequence of part of the foregoing DNA, an oligonucleotide DNA having the nucleotide sequence of 5 to 60 consecutive bases in the foregoing DNA, and preferably an oligonucleotide DNA having the nucleotide sequence of 10 to 40 consecutive bases therein. Furthermore, they include a shear stress-responsive DNA capable of hybridizing with the foregoing DNA or a fragment thereof under stringent conditions.

[0139] The most accurate test for evaluating the presence or absence of a mutation causative of arteriosclerosis in the locus of a shear stress-responsive gene is a direct comparison of the genes from a control population with the genes from arteriosclerotic patients.

[0140] Specifically, human biological specimens such as vascular endothelium, blood serum or saliva, or specimens derived from primary cultured cells established from the biological specimens, are collected from 10 to 100 arteriosclerotic patients and healthy subjects. Then, DNA is extracted from each of the biological specimens or the primary cultured cell-derived specimens (this DNA is hereinafter referred to as the specimen-derived DNA). This specimen-derived DNA may be used directly, or may be used by amplifying a shear stress-responsive DNA using primers designed on the basis of the nucleotide sequence possessed by the DNA of the present invention. Alternatively, PCR may be carried out by using a template comprising the specimen-derived cDNA and primers designed on the basis of the nucleotide sequence possessed by the DNA of the present invention. Thus, a DNA fragment comprising a shear stress-responsive DNA sequence can be amplified and used.

[0141] In order to determine whether the DNA of the present invention has a mutation causative of arteriosclerosis, a method for detecting a heteroduplex formed by hybridization between a DNA strand having a wild type allele and a DNA strand having a mutated allele can be used.

[0142] The methods which can be used to detect a heteroduplex include (1) the detection of a heteroduplex by polyacrylamide electrophoresis [Trends Genet., 7, 5(1991)], (2) single strand conformation polymorphism analysis [Genomics, 16, 325-332(1993)], (3) chemical cleavage of mismatches (CCM), (4) enzymatic cleavage of mismatches

[Nature Genetics, 9, 103-104(1996)], (5) denaturing gradient gel electrophoresis [Mutat. Res., 288, 103-112(1993)], and the like.

[0143] Using a template comprising the specimen-derived DNA or specimen-derived cDNA and primers designed on the basis of the sequence possessed by the DNA of the present invention, a shear stress-responsive DNA is amplified as a fragment smaller than 200 bp, and then subjected to polyacrylamide electrophoresis. If a heteroduplex is formed owing to a mutation of the shear stress-responsive DNA, it has lower mobility than a homoduplex having no mutation, and can hence be detected as extra bands. The use of a specially made gel (Hydro-link, MDE or the like) provides a higher degree of separation. The analysis of a fragment smaller than 200 bp makes it possible to detect an insertion, a deletion, and most one-base substitutions. It is desirable to carry out this heteroduplex analysis on one sheet of gel in combination with single strand conformation polymorphism analysis as described below.

[0144] In single strand conformation polymorphism analysis (SSCP analysis), a shear stress-responsive DNA is amplified as a fragment smaller than 200 bp by using a template comprising the specimen-derived DNA or specimen-derived cDNA and primers designed on the basis of the sequence possessed by the DNA of the present invention. The amplified shear stress-responsive DNA fragment is denatured and then electrophoresed through native polyacrylamide gel. During DNA amplification, the primers are labeled with an isotope or fluorochrome, or the unlabeled amplification product is stained with silver. Thus, the amplified shear stress-responsive DNA fragment can be detected as bands. In order to clarify the difference from a wild type pattern, a control specimen may be electrophoresed at the same time. Thus, fragments having a mutation can be detected owing to their difference in mobility.

[0145] In chemical cleavage of mismatches (CCM), the shear stress-responsive DNA is amplified by using a template comprising the specimen-derived DNA or specimen-derived cDNA and primers designed on the basis of the sequence possessed by the DNA of the present invention. The amplified DNA fragment is hybridized with a labeled DNA prepared by incorporating an isotope or fluorescent label into the DNA of the present invention, and treated with osmium tetroxide to cleave one strand of the DNA at a mismatching site. Thus, a mutation can be detected. CCM is one of the most sensitive detection methods and can be applied even to specimens of kilobase length.

[0146] In place of the aforesaid osmium tetroxide, a combination of an enzyme involved in the repair of mismatches in cells (e.g., T4 phage resolvase or endonuclease VII) and RNase A may be used. Thus, a mismatch can be cleaved enzymatically.

[0147] In denaturing gradient gel electrophoresis (DGGE), the shear stress-responsive DNA is amplified by using a template comprising the specimen-derived DNA or specimen-derived cDNA and primers designed on the basis of the sequence possessed by the DNA of the present invention. The amplified DNA fragment is electrophoresed through a gel having a concentration gradient of a chemical denaturing agent or a temperature gradient. The amplified DNA fragment moves through the gel up to a position where it is denatured into single strands, and cease to move after denaturation. Since the amplified DNA fragments move through the gel differently according to the presence or absence of a mutation in the shear stress-responsive DNA, the presence of a mutation can be detected. In order to enhance detection sensitivity, a poly(G:C) terminus may be attached to each primer.

[0148] Another method for determining whether the DNA of the present invention has a mutation causative of arteriosclerosis is a protein truncation test (PTT) [Genomics, 20, 1-4(1994)]. This test can specifically detect a frame shift mutation, splice site mutation or nonsense mutation which develops a deletion in protein. In PTT, a special primer is designed by linking a T7 promoter sequence and a eucaryotic translation initiation sequence to the 5'-terminus of the DNA of the present invention. Using this primer, cDNA is prepared from specimen-derived RNA according to the reverse-transcribed PCR (RT-PCR) technique. When this cDNA is reacted in an *in vitro* transcription/translation system, it is transcribed into mRNA by the action of T7 promoter and translated by the action of the translation initiation sequence, so that a protein is produced. When this protein is electrophoresed through a gel, there will be no mutation that develops a deletion if the position of the migrated protein corresponds to that of the full-length protein. If the protein has a deletion, it will be migrated over a shorter distance than the full-length protein. Thus, the degree of deletion can be estimated from that position.

[0149] In order to determine the nucleotide sequences of the specimen-derived DNA and the specimen-derived cDNA, it is possible to use primers designed on the basis of the nucleotide sequence of the DNA of the present invention. An analysis of the determined nucleotide sequences makes it possible to judge whether or not the specimen-derived DNA or the specimen-derived cDNA has a mutation causative of arteriosclerosis.

[0150] A mutation outside the coding region of a shear stress-responsive gene can be detected by testing non-coding regions such as introns and control sequences near or within the gene. An arteriosclerotic disease caused by a mutation in a non-coding region can be ascertained by comparing the test specimen with a control specimen according to the above-described method and detecting an abnormal size, or abnormal production, of mRNA in the arteriosclerotic patient.

[0151] For the gene suggesting the presence of a mutation in a non-coding region, the DNA of the non-coding region can be cloned by using the DNA of the present invention as a probe for hybridization. A mutation in a non-coding region may be searched according to any of the above-described methods.

[0152] By subjecting to a statistical analysis according to the method described in Handbook of Human Genetics. Linkage, The John Hopkins University Press, Baltimore (1994), the mutations so found may be identified as single nucleotide polymorphisms (SNPs) having a linkage with arteriosclerosis. Moreover, a gene causative of arteriosclerosis may be identified by obtaining DNA from a family having a history of arteriosclerosis according to the previously described method, and detecting a mutation therefrom.

[0153] Now, the method for diagnosing vascular diseases caused by arteriosclerosis using the shear stress-responsive DNA of the present invention is described below.

[0154] The DNAs which can be used in this method include, for example, DNAs having the nucleotide sequences represented by SEQ ID NO:1,3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 116, 117, 119, 121, 123, 125, 127, 129, 130, 131, 132, 133, 134, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 168, 170, 172 and the like. Moreover, they include a DNA having a sequence of part of the foregoing DNA, an oligonucleotide DNA having the nucleotide sequence of 5 to 60 consecutive bases in the foregoing DNA, and preferably an oligonucleotide DNA having the nucleotide sequence of 10 to 40 consecutive bases therein. Furthermore, they include a shear stress-responsive DNA capable of hybridizing with the foregoing DNA or a fragment thereof under stringent conditions.

[0155] The cause of arteriosclerosis can be ascertained by detecting a gene mutation in any tissue of a human subject. For example, where a mutation is present in the germ cell system, an individual having inherited the mutation may tend to develop arteriosclerosis. The mutation can be identified by testing DNA obtained from any tissue of the body of the individual. For example, a diagnosis of arteriosclerosis can be made by collecting blood from a subject, extracting DNA from cells of the blood, and using this DNA to perform a test for a gene mutation. Moreover, a prenatal diagnosis may be made by using fetal cells, placental cells or amniotic cells to perform a test for a gene mutation.

[0156] Furthermore, by obtaining a biological tissue from the lesion of a patient having developed a vascular disease and testing its DNA, the type of the vascular disease can be diagnosed and the results thus obtained can be utilized to select a drug to be administered. In order to detect a mutation of a gene in the tissue, it is useful to isolate the lesional tissue segregated from the surrounding normal tissues. An arteriosclerotic lesion may be obtained, for example, by a bypass operation for replacing the lesion of arteriosclerosis with a normal blood vessel. The tissue thus obtained is treated with trypsin or the like, and the resulting cells are cultured in a suitable culture medium. Then, chromosomal DNA and mRNA can be extracted from the cultured cells.

[0157] The DNA obtained from a human specimen for diagnostic purposes according to any of the aforesaid methods is hereinafter referred to as the diagnostic specimen-derived DNA. Moreover, the cDNA synthesized from the RNA obtained from a human specimen for diagnostic purposes according to any of the aforesaid methods is hereinafter referred to as the diagnostic specimen-derived cDNA.

[0158] Using the shear stress-responsive DNA of the present invention and the diagnostic specimen-derived DNA or the diagnostic specimen-derived cDNA, a diagnosis of arteriosclerosis may be made according to the above-described method for detecting a gene causative of arteriosclerosis.

[0159] Moreover, in order to make a diagnosis of arteriosclerosis by using the shear stress-responsive DNA of the present invention and the diagnostic specimen-derived DNA or the diagnostic specimen-derived cDNA, there may also be employed a method such as (1) the detection of a restriction enzyme site, (2) the utilization of an allele-specific oligonucleotide probe [allele-specific oligonucleotide hybridization (ASO)], (3) PCR using an allele-specific oligonucleotide [amplification refractory mutation system (ARMS)], (4) oligonucleotide ligation assay (OLA), (5) PCR-preferential homoduplex formation assay (PCR-PHFA), or (6) oligo-DNA array [Protein-Nucleic Acid-Enzyme (in Japanese), 43, 2004-2011(1998)].

[0160] Where a restriction enzyme site disappears or appears as a result of a single base change, the mutation may be easily detected by amplifying the diagnostic specimen-derived DNA or the diagnostic specimen-derived cDNA with primers designed on the basis of the sequence possessed by the DNA of the present invention, digesting it with the restriction enzyme, and comparing the resulting restriction enzyme-cleaved DNA fragments with those obtained from healthy subjects. However, the occurrence of such a mutation is rare. For diagnostic purposes, a mismatch exerting no influence on annealing is introduced into PCR primers designed on the basis of the sequence possessed by the DNA of the present invention. Thus, for a mutation not accompanied by the disappearance or appearance of a restriction enzyme site, a restriction enzyme site is artificially introduced.

[0161] A short synthetic DNA probe hybridizes only with a perfectly base pairing sequence alone. Taking advantage of this characteristic, a single-base mutation can be easily detected by preparing an allele-specific oligonucleotide probe (ASO). For diagnostic purposes, reverse dot blotting is often employed in which an oligonucleotide designed on the basis of the sequence possessed by the DNA of the present invention and an identified mutation is attached to a filter and hybridization is carried out with a probe prepared from the diagnostic specimen-derived DNA or the diagnostic specimen-derived cDNA by PCR using primers designed on the basis of the sequence possessed by the DNA of the present invention and labeled dNTP. In the DNA chip method, an oligonucleotide designed on the basis of the sequence

possessed by the DNA of the present invention and the mutation is synthesized directly on a substrate (e.g., slide glass or silicon) to form a highly dense array. This DNA chip method is a mutation detection method suitable for large-scale diagnostic purposes because various mutations can be more conveniently detected by using a small amount of the diagnostic specimen-derived DNA or the diagnostic specimen-derived cDNA.

[0162] Nucleotide mutations can also be detected by the following oligonucleotide ligation assay (OLA).

[0163] Two oligonucleotides consisting of about 20 bases, which are designed from the sequence possessed by the DNA of the present invention and are capable of hybridizing on both sides of a mutation site, are prepared. Using a template comprising the diagnostic specimen-derived DNA or the diagnostic specimen-derived cDNA and primers designed from the sequence possessed by the DNA of the present invention, shear stress-responsive DNA fragment is amplified by PCR. The amplified fragment is hybridized with the aforesaid polynucleotide. After hybridization, the two oligonucleotides are ligated by means of DNA ligase. For example, by labeling one oligonucleotide with biotin and the other oligonucleotide with a different label such as digoxigenin, it is possible to detect rapidly whether the ligation has occurred or not. OLA is a mutation detection method suitable for large-scale diagnostic purposes because it does not require electrophoresis or centrifugation.

[0164] A very small amount of a mutated gene can also be quantitatively and easily detected by the following PCR-PHFA.

[0165] PCR-PHFA is a combination of three techniques including gene amplification (PCR), liquid-phase hybridization exhibiting very high specificity, and enzymatic detection of PCR product (ED-PCR) detecting the PCR product in the same manner as ELISA. Using a dinitrophenyl(DNP)-labeled and biotin-labeled primer set, an amplification product labeled at both ends is prepared by carrying out PCR amplification while using the DNA of the present invention as a template. This amplification product is mixed with a large excess (20- to 100-fold) of an unlabeled amplification product obtained by using an unlabeled primer set having the same sequences and a template comprising the diagnostic specimen-derived DNA or the diagnostic specimen-derived cDNA. After thermal denaturation, this mixture is cooled with a gentle temperature gradient of the order of 1°C/5-10 minutes to form perfect complementary strands preferentially. The labeled DNA so reformed is captured and adsorbed to a streptavidin-immobilized well via biotin. On the other hand, an enzyme-labeled anti-DNP antibody is bound thereto via DNP. Thus, the labeled DNA can be detected by a color-developing reaction based on the enzyme. If a gene having the same sequence as the labeled DNA is not present in the specimen, the original double-strand labeled DNA is preferentially reformed to develop a color. In contrast, if a gene having the same sequence is present in the specimen, complementary strands are randomly replaced to decrease the reformation of the labeled DNA, resulting in a marked reduction in color development. Thus, known mutated polymorphic genes can be detected and quantitatively determined.

[0166] Now, the methods for detection and quantitative determination of the shear stress-responsive protein of the present invention immunologically using the antibody of the present invention are described below.

[0167] The methods by which a microorganism, an animal cell or an insect cell, or a tissue, expressing the protein of the present invention intracellularly or extracellularly can be immunologically detected and determined quantitatively using the antibody (polyclonal antibody or monoclonal antibody) of the present invention include fluorescent antibody technique, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunohistochemical staining techniques (e.g., ABC method and CSA method) such as tissue immunostaining and cell immunostaining, western blotting, dot blotting, immunoprecipitation, sandwich ELISA [Experimental Manual for Monoclonal Antibodies (in Japanese), Kodansha Scientific (1987); Biochemical Experimental Lectures (Second Series) 5, Methods of Immunobiochemical Research (in Japanese), Tokyo-Kagaku-Dojin (1986)], and the like.

[0168] The fluorescent antibody technique is a technique in which, after a microorganism, an animal cell or an insect cell, or a tissue, expressing the protein of the present invention intracellularly or extracellularly is reacted with the antibody of the present invention and further reacted with an anti-mouse IgG antibody, or a fragment thereof, labeled with a fluorescent material such as fluorescein isothiocyanate (FITC), fluorescence is measured with a flow cytometer.

[0169] Enzyme-linked immunosorbent assay (ELISA) is a technique in which, after a microorganism, an animal cell or an insect cell expressing the protein of the present invention intracellularly or extracellularly is reacted with the antibody of the present invention and further reacted with an anti-mouse IgG antibody, or a binding fragment thereof, labeled with an enzyme such as peroxidase or biotin, the developed color is measured with a spectrophotometer.

[0170] Radioimmunoassay (RIA) is a technique in which, after a microorganism, an animal cell or an insect cell, or a tissue, expressing the protein of the present invention intracellularly or extracellularly is reacted with the antibody of the present invention and further reacted with an anti-mouse IgG antibody, or a fragment thereof, labeled with a radioactive substance, radioactivity is measured with a scintillation counter or the like.

[0171] Cell immunostaining and tissue immunostaining are in which, after a microorganism, an animal cell or an insect cell, or a tissue, expressing the protein of the present invention intracellularly or extracellularly is reacted with the antibody of the present invention and further reacted with an anti-mouse IgG antibody, or a fragment thereof, labeled with a fluorescent material (e.g., FITC) or an enzyme (e.g., peroxidase or biotin), it is observed under the microscope.

[0172] Western blotting is a technique in which, after an extract of a microorganism, an animal cell or an insect cell,

or a tissue, expressing the protein of the present invention intracellularly or extracellularly is fractionated by SDS-polyacrylamide gel electrophoresis [Antibodies-A Laboratory Manual, Cold Spring Harbor Laboratory (1988)], this gel is blotted to a PVDF membrane or a nitrocellulose membrane, then the membrane is reacted with the antibody of the present invention and further reacted with an anti-mouse IgG antibody, or a fragment thereof, labeled with a fluorescent material (e.g., FITC) or an enzyme (e.g., peroxidase or biotin). Thus, the protein of the present invention can be detected.

[0173] Dot blotting is a technique in which, after an extract of a microorganism, an animal cell or an insect cell, or a tissue, expressing the protein of the present invention intracellularly or extracellularly is blotted to a nitrocellulose membrane, this membrane is reacted with the antibody of the present invention and further reacted with an anti-mouse IgG antibody, or a binding fragment thereof, labeled with a fluorescent material (e.g., FITC) or an enzyme (e.g., peroxidase or biotin). Thus, the protein of the present invention can be detected.

[0174] Immunoprecipitation is a technique in which, after an extract of a microorganism, an animal cell or an insect cell, or a tissue, expressing the protein of the present invention intracellularly or extracellularly is extracted, the resulting extract is reacted with the antibody of the present invention, a carrier having the ability to bind specifically to immunoglobulin (e.g., protein G-Sepharose) is added thereto so as to precipitate the resulting antigen-antibody complex.

[0175] In sandwich ELISA, two antibodies of the present invention having different antigen recognition sites are provided. In advance, one of the antibodies is adsorbed to a plate, and the other is labeled with a fluorescent material (e.g., FITC) or an enzyme (e.g., peroxidase or biotin). After an extract of a microorganism, an animal cell or an insect cell, or a tissue, expressing the protein of the present invention intracellularly or extracellularly is extracted, the resulting extract is reacted with the antibody-adsorbed plate, the plate is reacted with the labeled antibody and subjected to a reaction depending on the labeling material.

[0176] Now, the method for diagnosing vascular diseases caused by arteriosclerosis using the antibody of the present invention is described below.

[0177] The identification of an alteration of the expression level of a shear stress-responsive protein and a structural change of the expressed protein in human biological specimens and human primary cultured cells is useful in knowing the risk of developing arteriosclerosis in the future or the cause of an already developed vascular disease.

[0178] The methods which can be employed to make a diagnosis by detecting the expression level of a shear stress-responsive protein and a structural change thereof include the above-described fluorescent antibody technique, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunohistochemical staining techniques (e.g., ABC method and CSA method) such as tissue immunostaining and cell immunostaining, western blotting, dot blotting, immunoprecipitation, sandwich ELISA and the like.

[0179] The materials which can be diagnosed by the aforesaid methods include biological specimens themselves (e.g., blood vessels in the lesion, blood, serum, urine, feces and saliva) collected from human subjects, and cells or cell extracts obtained from the foregoing biological specimens. Alternatively, an isolated paraffin or cryostat section of a tissue obtained from biological specimens may also be used.

[0180] Now, the methods for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using the shear stress-responsive DNA of the present invention, a protein encoded by the DNA, or an antibody capable of recognizing the protein are described below.

[0181] The DNAs which can be used in these screening methods include, for example, DNAs having the nucleotide sequences represented by SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 116, 117, 119, 121, 123, 125, 127, 129, 130, 131, 132, 133, 134, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 168, 170, 172 and the like; and a shear stress-responsive DNA capable of hybridizing with the foregoing DNA or a fragment thereof under stringent conditions. The protein which can be used therein include a protein encoded by the foregoing DNA (e.g., a protein having an amino acid sequence selected from the amino acid sequences represented by SEQ ID NO: 144, 146, 148, 150, 152, 154, 156, 158, 169, 171 and 173); and a protein comprising an amino acid sequence in which one or more amino acids are deleted, replaced or added as compared with the amino acid sequence possessed by the foregoing protein, and having an activity involved in the formation of an arteriosclerotic lesion. The antibody which can be used therein include an antibody capable of recognizing the foregoing protein.

[0182] A microorganism, an animal cell or an insect cell transformed by introducing the DNA of the present invention so as to produce the protein of the present invention or a partial polypeptide of the protein, and the protein or polypeptide in purified form, are useful for the purpose of screening an agent acting specifically on a shear stress-responsive protein. The agent obtained by this screening is useful for the treatment of vascular diseases caused by arteriosclerosis.

[0183] One of the aforesaid screening methods comprises selecting a labeled compound binding specifically to a microorganism, an animal cell or an insect cell transformed so as to produce the protein of the present invention or a partial polypeptide of the protein (hereinafter referred to as the transformant for screening). The specific binding of a labeled compound may be detected by comparison with a control comprising an untransformed microorganism, animal

cell or insect cell. Alternatively, an unlabeled compound may be selected by competitive screening in which its inhibitory effect on the binding to the transformant for screening of a compound or protein binding specifically to the transformant for screening is used as an index.

[0184] The purified protein of the present invention or the purified partial polypeptide of the protein may be used to select a labeled compound binding specifically to a shear stress-responsive protein. The binding of the labeled compound may be determined quantitatively according to the above-described immunological method using the antibody of the present invention. Alternatively, an unlabeled compound may be selected by competitive screening in which its inhibitory effect on the binding to the protein or polypeptide of a labeled compound binding to the protein or polypeptide is used as an index.

[0185] In the other of the aforesaid screening methods, a large number of partial peptides of the protein are densely synthesized on plastic pins or a certain solid support. Thus, a compound or protein binding selectively to the peptides can be efficiently screened (WO 84/03564).

[0186] An expression regulating agent capable of regulating the expression of a shear stress-responsive mRNA or protein in vascular endothelial cells is also useful for the treatment of vascular diseases caused by arteriosclerosis.

[0187] An agent for regulating the transcription or translation of a shear stress-responsive gene can be screened by adding various compounds to a vascular endothelial cell line and assaying an increase or decrease in the expression of a shear stress-responsive mRNA using the DNA of the present invention. An increase or decrease in the expression of a shear stress-responsive mRNA may be detected by the above-described PCR, Northern blotting, and RNase protection assay.

[0188] An agent for regulating the transcription or translation of a shear stress-responsive gene can also be screened by adding various compounds to a vascular endothelial cell line and assaying an increase or decrease in the expression of a shear stress-responsive protein using the antibody of the present invention. An increase or decrease in the expression of a shear stress-responsive protein may be detected by the above-described fluorescent antibody technique, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunohistochemical staining techniques (e.g., ABC method and CSA method) such as tissue immunostaining and cell immunostaining, western blotting, dot blotting, immunoprecipitation, and sandwich ELISA.

[0189] The compound obtained by the aforesaid methods may be administered, as an agent, to model animals for arteriosclerosis, such as ApoE knockout mice and rabbits fed with a high cholesterol diet. By measuring the incorporation of oxidized LDL and cholesterol into the vascular endothelium and the formation of an arteriosclerotic lesion in these animals, the therapeutic effect of the compound on the vascular disease caused by arteriosclerosis can be evaluated.

[0190] Now, the drug delivery method using the antibody of the present invention is described below.

[0191] The antibody used for this drug delivery may be any antibody in accordance with the present invention. However, it is particularly desirable to use a humanized antibody.

[0192] Usable humanized antibodies include a human chimeric antibody, a complementary determining region (hereinafter referred to as CDR) grafted humanized antibody, and the like.

[0193] The human chimeric antibody means an antibody consisting of a heavy-chain variable region (the heavy chain may hereinafter be referred to as H chain, the variable region as V region, and the heavy-chain variable region as HV or VH) and a light-chain variable region (the light chain may hereinafter be referred to as L chain, and the light-chain variable region as LV or VL) of an antibody of an animal other than human, and a heavy-chain constant region (the constant region may hereinafter be referred to as C region, and the heavy-chain constant region as CH) and a light-chain constant region (the light-chain constant region may hereinafter be referred to as CL) of a human antibody. As the animal other than human, there may be used any of various animals that permit the generation of hybridomas, such as mice, rats, hamsters and rabbits.

[0194] The human chimeric antibody of the present invention may be produced by obtaining cDNAs encoding VH and VL from a hybridoma capable of producing a monoclonal antibody which binds to the protein of the present invention and neutralizes the action of the protein of the present invention; inserting them into an expression vector for mammalian cells having genes encoding human antibody CH and human antibody CL, respectively, to construct a human chimeric antibody expression vector; and introducing the vector into mammalian cells to express the antibody.

[0195] The CH of the human chimeric antibody may be any CH belonging to human immunoglobulin (hereinafter abbreviated as hlg). However, the CH of hlgG class is preferred. Furthermore, there may be used any of various subclasses (e.g., hlgG1, hlgG2, hlgG3 and hlgG4) belonging to hlgG class. The CL of the human chimeric antibody may be any CL belonging to hlg, and the CL of κ or λ class may be used.

[0196] The CDR-grafted humanized antibody means an antibody in which the amino acid sequences of CDRs of VH and VL of an antibody of an animal other than human are transplanted into appropriate positions of VH and VL of a human antibody.

[0197] The CDR-grafted humanized antibody of the present invention may be produced by constructing cDNAs encoding V regions in which the CDR sequences of VH and VL of any human antibody are replaced by the CDR sequences

of VH and VL, respectively, of an antibody of an animal other than human that reacts with the protein of the present invention, binds to the protein of the present invention, and neutralizes the action of the protein of the present invention; inserting them into an expression vector for mammalian cells having genes encoding human antibody CH and human antibody CL, respectively, to construct a CDR-grafted humanized antibody expression vector; and introducing the

vector into animal cells to express the antibody.
[0198] The CH of the CDR-grafted humanized antibody may be any CH belonging to hlg. However, the CH of hlgG class is preferred. Furthermore, there may be used any of various subclasses (e.g., hlgG1, hlgG2, hlgG3 and hlgG4) belonging to hlgG class. The CL of the CDR-grafted humanized antibody may be any CL belonging to hlg, and the CL of κ or λ class may be used.

[0199] Originally, human antibodies mean antibodies existing naturally in the human body. However, they also include antibodies obtained from a human antibody phage library and a human antibody-producing transgenic animal which have been created on the basis of the recent progress of genetic engineering, cell technology and embryological engineering.

[0200] An antibody existing in the human body may be obtained, for example, according to the following method.

[0201] Lymphocytes are isolated from human peripheral blood, immortalized by infection with EB virus or the like, and then cloned. After the selected lymphocyte producing a desired antibody is cultured, the antibody can be obtained from the resulting culture.

[0202] The human antibody phage library is a library in which an antibody gene prepared from human B cells is inserted into a phage gene so as to express antibody fragments (e.g., Fab and single-chain antibody) on the phage surface. From this library, a phage expressing an antibody fragment having a desired antigen-binding activity can be recovered by using its binding activity for a substrate having the antigen immobilized thereon as an index. This antibody fragment can further be converted into a complete human antibody according to genetic engineering techniques.

[0203] The human antibody-producing transgenic animal means an animal in which a human antibody gene is introduced into the cells. Specifically, a human antibody-producing transgenic animal may be created by introducing a human antibody gene into a mouse ES cell, transplanting the ES cell into an early embryo of another mouse, and developing the embryo. In order to prepare a human antibody from the human antibody-producing transgenic animal, there may be employed a method which comprises obtaining a human antibody-producing hybridoma according to the common method for the formation of hybridomas in mammals other than human, and culturing the hybridoma to produce and accumulate the human antibody in the resulting culture.

[0204] The antibody fragments include Fab, Fab', F(ab')₂, single-chain antibody, dsFv, CDR-containing peptides, and the like.

[0205] Among the fragments obtained by treating IgG with the proteolytic enzyme papain (IgG is cleaved at the 224th amino acid residue of each H chain), Fab is an antibody fragment with a molecular weight of about 50,000 which has an antigen-binding activity and consists of about a half of an H chain on the N-terminal side and a whole L chain which are linked together via a disulfide bond.

[0206] The Fab of the present invention may be obtained from an antibody reacting specifically with the protein of the present invention, by treating it with the proteolytic enzyme papain. Alternatively, Fab may also be obtained by inserting DNA encoding the Fab of the antibody into a procaryotic expression vector or a eucaryotic expression vector, and introducing the resulting vector into a procaryote or eucaryote to express the DNA.

[0207] Among the fragments obtained by treating IgG with the proteolytic enzyme pepsin (IgG is cleaved at the 234th amino acid residue of each H chain), F(ab')₂ is an antibody fragment with a molecular weight of about 100,000 which has an antigen-binding activity and is slightly larger than two Fab molecules linked together via disulfide bonds in the hinge area.

[0208] The F(ab')₂ of the present invention may be obtained from an antibody reacting specifically with the protein of the present invention, by treating it with the proteolytic enzyme pepsin. Alternatively, F(ab')₂ may also be obtained by inserting DNA encoding the F(ab')₂ of the antibody into a procaryotic expression vector or an eucaryotic expression vector, and introducing the resulting vector into a procaryote or eucaryote to express the DNA.

[0209] Fab' is an antibody fragment with a molecular weight of about 50,000 which has an antigen-binding activity and is obtained by breaking the disulfide bonds in the hinge area of the aforesaid F(ab')₂.

[0210] The Fab' of the present invention may be obtained from an antibody reacting specifically with the protein of the present invention, by treating it with the reducing agent dithiothreitol. Alternatively, Fab' may also be obtained by inserting DNA encoding the Fab' fragment of the antibody into a procaryotic expression vector or an eucaryotic expression vector, and introducing the resulting vector into a procaryote or eucaryote to express the DNA.

[0211] A single-chain antibody (hereinafter also referred to as scFv) is a VH-P-VL or VL-P-VH polypeptide consisting of one VH and one VL linked together by a suitable peptide linker (hereinafter referred to as P). The VH and VL contained in the scFv used in the present invention may be those of any antibody (e.g., humanized antibody or human antibody) reacting specifically with the protein of the present invention.

[0212] The single-chain antibody of the present invention may be obtained according to the following method.

[0213] After cDNAs encoding the VH and VL of an antibody reacting specifically with the protein of the present invention are obtained, a DNA encoding the single-chain antibody is constructed. Then, the single-chain antibody may be obtained by inserting the DNA into a procaryotic expression vector or an eucaryotic expression vector, and introducing the resulting vector into a procaryote or eucaryote to express the DNA.

5 [0214] The disulfide-stabilized V region fragment (hereinafter referred to as dsFv) is a fragment obtained by replacing one amino acid residue of each of VH and VL with a cysteine residue and linking these polypeptides together by a disulfide bond extending between the cysteine residues. The amino acid residues to be replaced with cysteine residues can be selected on the basis of the predicted stereostructure of the antibody, according to the method shown by Reiter et al. [Protein Engineering, 7, 697(1994)]. The VH and VL contained in the disulfide-stabilized V region fragment used
10 in the present invention may be those of any antibody (e.g., humanized antibody or human antibody) reacting specifically with the protein of the present invention.

[0215] The disulfide-stabilized V region fragment of the present invention may be obtained according to the following method.

15 [0216] After cDNAs encoding the VH and VL of an antibody reacting specifically with the protein of the present invention are obtained, a DNA encoding the disulfide-stabilized V region fragment is constructed. Then, the disulfide-stabilized V region fragment may be obtained by inserting the DNA into a procaryotic expression vector or an eucaryotic expression vector, and introducing the resulting vector into a procaryote or eucaryote to express the DNA.

[0217] The CDR-containing peptides may be prepared by chemical synthesis processes such as the Fmoc method and the tBoc method.

20 [0218] A conjugated antibody prepared from the antibody of the present invention as described below may be used as a drug delivery system to deliver an agent or protein specifically to a lesion of arteriosclerosis.

[0219] The conjugated antibody is an antibody obtained by linking a radioactive isotope, protein, low-molecular-weight agent or the like to an antibody reacting specifically with the protein of the present invention (e.g., a humanized antibody, a human antibody, or a fragment of these antibodies) by chemical means or genetic engineering means.

25 [0220] The conjugated antibody of the present invention may be prepared by linking a radioactive isotope, protein, low-molecular-weight agent or the like to N-terminal or C-terminal side of an H chain or L chain of an antibody or antibody fragment reacting specifically with the protein of the present invention, to a suitable substituent group or side chain of the antibody or antibody fragment, or to a sugar chain of the antibody or antibody fragment, by chemical means or genetic engineering means.

30 [0221] Usable radioactive isotopes include ^{131}I , ^{125}I and the like. They can be linked to an antibody or an antibody fragment, for example, according to the chloramine T method.

[0222] Usable low-molecular-weight agents are anticancer drugs including, for example, alkylating agents such as nitrogen mustard and cyclophosphamide; antimetabolites such as 5-fluorouracil and methotrexate; antibiotics such as daunomycin, bleomycin, mitomycin C, daunorubicin and doxorubicin; plant alkaloids such as vincristine, vinblastine
35 and vindesine; and hormones such as tamoxifen and dexamethasone [Clinical Oncology (in Japanese), edited by the Japanese Society for the Research of Clinical Oncology, 1996, Gan-to-Kagakuryoho Sha]; anti-inflammatory drugs including, for example, steroids such as hydrocortisone and prednisone; nonsteroidal anti-inflammatory drugs such as aspirin and indomethacin; immunomodulators such as gold sodium thiomalate and penicillamine; immunosuppressants such as cyclophosphamide and azathioprine; and antihistamines such as chlorpheniramine maleate and clemastine
40 [Inflammation and Anti-inflammatory Therapy (in Japanese), 1982, Ishiyaku Shuppan Kabushiki Kaisha]; and the like.

[0223] A low-molecular-weight agent may be linked to the aforesaid antibody in the usual manner. For example, daunomycin may be linked to the antibody, for example, by linking daunomycin to an amino group of the antibody via glutaraldehyde, or by linking the amino group of daunomycin to a carboxyl group of the antibody via water-soluble carbodiimide.

45 [0224] Suitable proteins include cytokines activating immunocompetent cells, and growth controlling factors for vascular endothelium, vascular smooth muscle and the like. Examples thereof include human interleukin 2, human granulocyte macrophage colony-stimulating factor, human macrophage colony-stimulating factor, human interleukin 12, fibroblast growth factor 2 (FGF-2) and platelet-derived growth factor (PDGF). Moreover, in order to damage directly with proliferative vascular smooth muscle cells of an arteriosclerotic lesion, there may be used a toxin such as ricin or
50 diphtheria toxin.

[0225] The conjugated antibody having a protein linked thereto may be prepared according to the following method.

[0226] A DNA encoding the conjugated antibody is constructed by linking cDNA encoding the protein to cDNA encoding the antibody or antibody fragment. After this DNA is inserted into a procaryotic or eucaryotic expression vector, the resulting expression vector is introduced into a procaryote or eucaryote to express the DNA. Thus, the desired
55 conjugated antibody can be obtained.

[0227] Now, the method of gene therapy using a virus vector containing the shear stress-responsive DNA of the present invention is described below.

[0228] A therapeutic agent may be prepared from the above-described recombinant virus vector and a base for gene

therapeutic agents [Nature Genet., 8, 42(1994)].

[0229] The base for gene therapeutic agents may be any base that is commonly used for injections. Examples thereof include distilled water; a solution of a salt such as sodium chloride or a mixture of sodium chloride and an inorganic salt; a solution of mannitol, lactose, dextran, glucose or the like; a solution of an amino acid such as glycine or arginine; and a mixture of an organic acid solution or a salt solution and a glucose solution. Moreover, injections in the form of solutions, suspensions or dispersions may be prepared in the usual manner, by using auxiliaries such as osmotic pressure regulators, pH regulators, vegetable oils (e.g., sesame oil and soybean oil) and surfactants (e.g., lecithin and nonionic surfactants), in combination with the aforesaid bases. These injections may also be prepared as preparations to be dissolved at the time of use, according to a technique such as powdering or freeze-drying. Where the gene therapeutic agent of the present invention is a liquid, it may be used directly for therapeutic purposes, as required. Where it is a solid, it may be dissolved immediately before gene therapy in the aforesaid base having been sterilized as required, and used for therapeutic purposes. In order to administer the gene therapeutic agent of the present invention, there may be employed a local administration method using a double balloon catheter or the like so that the gene therapeutic agent will be absorbed into the vascular endothelium of the treated site of the patient.

[0230] As a method for carrying a virus vector more specifically to an arteriosclerotic lesion, Somlia et al. have reported a method using a fusion protein consisting of a single-chain antibody capable of recognizing specifically the LDL receptor and the Env protein of a retrovirus vector [Proc. Natl. Acad. Sci. USA, 92, 7570-7574(1995)]. This system is not limited to retrovirus vectors, but may also be applied to lentivirus vectors and the like.

[0231] The nonviral gene transfer techniques which are known in this field include calcium phosphate coprecipitation [Virology, 52, 456-467(1973); Science, 209, 1414-1422(1980)], microinjection [Proc. Natl. Acad. Sci. USA, 77, 5399-5403(1980); Proc. Natl. Acad. Sci. USA, 77, 7380-7384(1980); Cell, 27, 223-231(1981); Nature, 294, 92-94(1981)], membrane fusion-mediated transfer method using liposomes [Proc. Natl. Acad. Sci. USA, 84, 7413-7417(1987); Biochemistry, 28, 9508-9514(1989); J. Biol. Chem., 264, 12126-12129(1989); Hum. Gene Ther., 3, 267-275(1992); Science, 249, 1285-1288(1990); Circulation, 83, 2007-2011(1992)], direct DNA incorporation and receptor-mediated DNA transfer method [Science, 247, 1465-1468(1990); J. Biol. Chem., 266, 14338-14342(1991); Proc. Natl. Acad. Sci. USA, 87, 3655-3659(1991); J. Biol. Chem., 264, 16985-16987(1989); BioTechniques, 11, 474-485(1991); Proc. Natl. Acad. Sci. USA, 87, 3410-3414(1990); Proc. Natl. Acad. Sci. USA, 88, 4255-4259(1991); Proc. Natl. Acad. Sci. USA, 87, 4033-4037(1990); Proc. Natl. Acad. Sci. USA, 88, 8850-8854(1991); Hum. Gene Ther., 3, 147-154(1991)], and the like.

[0232] When gene transfer using a virus vector is combined with direct in vivo gene transfer using liposome delivery, the virus vector can be directed to an arteriosclerotic lesion.

[0233] In addition, a virus vector may also be prepared by combining a DNA of appropriate size in accordance with the present invention with a polylysine-conjugated antibody specific for adenovirus hexon protein to form a complex, and linking the resulting complex to an adenovirus vector. This virus vector attains target cells stably, is incorporated into the cells by the action of endosomes, and is decomposed in the cells. Thus, the gene can be expressed efficiently.

[0234] In an investigation on tumors, it has been reported that membrane fusion-mediated transfer method using liposomes permits a liposome preparation to be administered directly to a target tissue, and the tissue can hence incorporate and express the gene locally [Hum. Gene Ther., 3, 399-410(1992)]. Accordingly, it may be expected that a similar effect is produced in the case of an arteriosclerotic lesion. In order to deliver DNA directly to an arteriosclerotic lesion, it is preferable to employ a gene transfer technique. Receptor-mediated DNA transfer is carried out, for example, by conjugating DNA (usually taking the form of a covalently closed supercoiled plasmid) to a protein ligand via polylysine. The ligand is selected on the basis of the presence of the corresponding ligand receptor on the cell surface of the target cells or tissue. Examples of the combination of the receptor and the ligand include the combination of LDL receptor and LDL, and the combination of scavenger receptor and oxidized LDL. If desired, this ligand-DNA conjugate may be directly injected into the blood and thereby delivered to a target tissue where it binds to the receptor and the DNA-protein complex is internalized. In order to prevent the intracellular degradation of DNA, the target tissue may be simultaneously infected with an adenovirus to disrupt the endosome function.

[0235] Now, the method of treatment using an antibody capable of recognizing specifically the shear stress-responsive DNA of the present invention is described below.

[0236] A pharmaceutical containing the antibody of the present invention may be administered alone as a therapeutic agent. However, it is usually desirable to provide as pharmaceutical preparations produced by blending the antibody with one or more pharmacologically acceptable carriers and working up the resulting blend according to any of various techniques known well in the technical field of pharmaceuticals.

[0237] It is desirable to use the route of administration which is most effective for the purpose of treatment. Examples thereof include oral administration and parenteral administration such as buccal, intratracheal, intrarectal, subcutaneous, intramuscular and intravenous administration. In the case of antibody preparations, intravenous administration is desirable.

[0238] Examples of dosage forms include sprays, capsules, tablets, granules, medicated syrups, emulsions, sup-

positories, injections, ointments, tapes, and the like.

[0239] Pharmaceutical preparations suitable for oral administration include emulsions, medicated syrups, capsules, tablets, powders, granules and the like.

[0240] Liquid preparations such as emulsions and medicated syrups may be produced using additives including water; sugars such as sucrose, sorbitol and fructose; glycols such as polyethylene glycol and propylene glycol; oils such as sesame oil, olive oil and soybean oil; antiseptics such as p-hydroxybenzoic acid esters; flavors such as strawberry flavor and peppermint; and the like.

[0241] Capsules, tablets, powders, granules and the like may be produced using additives including excipients such as lactose, glucose, sucrose and mannitol; disintegrators such as starch and sodium alginate; lubricants such as magnesium stearate and talc; binders such as polyvinyl alcohol, hydroxypropylcellulose and gelatin; surfactants such as fatty acid esters; plasticizers such as glycerin; and the like.

[0242] Pharmaceutical preparations suitable for parenteral administration include injection, suppository, spray and the like. Injection is prepared using a carrier comprising a salt solution, a glucose solution or a mixture thereof, and the like. Alternatively, a powder for injection may be prepared by freeze-drying the antibody of the present invention in the usual manner and adding sodium chloride thereto. Suppository is prepared using a carrier such as cacao butter, hydrogenated fats and carboxylic acids.

[0243] Spray is prepared by using the antibody of the present invention itself, or using a carrier which does not irritate the mucous membranes of the oral cavity and respiratory tract of the patient and enables the antibody of the present invention to be dispersed as fine particles and easily absorbed, and the like.

[0244] Specific examples of the carrier include lactose and glycerin. Depending on the antibody of the present invention and the nature of the carrier used, aerosols, dry powders and the like may be prepared. Also in these parenteral preparations, the ingredients described as additive in connection with oral preparations may be added.

[0245] The dosage and the frequency of administration may vary according to the desired therapeutic effect, the method of administration, the period of treatment, the age and body weight of the patient, and the like. However, the drugs of the present invention are usually administered to adults in a daily dose of 10 µg/kg to 20 mg/kg.

[0246] One of the activities involved in an arteriosclerotic lesion (i.e. the activities regulating the development of arteriosclerosis) is the promotion or suppression of the apoptosis of vascular endothelial cells. Since it is known that, in vascular endothelial cells, the application of a shear stress tends to suppress the apoptosis of endothelial cells, the shear stress-responsive DNA of the present invention is considered to contain a gene and protein which exhibits a shear stress-dependent increase of expression in vascular endothelial cells and has an apoptosis-suppressing activity. Accordingly, by using this DNA containing a gene having an apoptosis-suppressing activity, a protein encoded by the DNA, a recombinant virus vector constructed by inserting the DNA into a vector, an antibody against the protein encoded by the DNA, and the like, the following applications can be made: (1) identification of the apoptosis sensitivity of cells, (2) regulation of the apoptosis of cells, and (3) screening of an agent for regulating the apoptosis of cells. These applications (1), (2) and (3) are described below in greater detail.

(1) Identification of the apoptosis sensitivity of cells

[0247] Now, the method for identifying the apoptosis sensitivity of cells using the shear stress-responsive DNA of the present invention or a protein encoded by the DNA is described below.

[0248] Apoptosis sensitivity means the degree of ease with which cells undergo apoptosis in response to an exogenous apoptotic stimulus, i.e. the degree of susceptibility of cells to the influence of an apoptotic stimulus. It is believed that this apoptosis sensitivity is defined according to whether the apoptotic signal in the cells is accompanied by a suppressive or promotive signal. The molecular entity thereof comprises a group of proteins involved in the suppression or promotion of apoptosis (e.g., apoptosis signal transduction molecule), i.e., the so-called apoptosis-related proteins. These apoptosis-related proteins include, for example, a protein encoded by the DNA (A4RS-041) having the nucleotide sequence represented by SEQ ID NO:7 of the present invention, and a protein having the amino acid sequence represented by SEQ ID NO:8.

[0249] Hemodynamic physical forces applied to vascular endothelial cells include a shear stress resulting from a flow of blood with fixed directionality (i.e., a laminar flow) and applied in parallel with the direction of the blood flow, and a normal stress caused by a blood pressure and applied perpendicularly to the endothelium. Vascular endothelial cells are always subjected to both forces. Generally, the development of arteriosclerosis is suppressed in regions where the shear stress is greater than the normal stress. Conversely, the development of arteriosclerosis tends to occur in regions where the normal stress is greater than the shear stress. In fact, it has been reported that the apoptosis of vascular endothelial cells is suppressed by a shear stress resulting from a laminar flow. In the culture system (i.e., the micro carrier/spinner flask system) used to obtain the DNAs of the present invention, not only a shear stress due to a flow, but also a normal stress due to a centrifugal force caused by rotation is applied to endothelial cells. Some of the genes responding to a shear stress are modified by a normal stress, and others are not modified thereby. This difference

in reactivity can be clarified by confirming the presence or absence of an increase of expression in HUVECs cultured in a parallel plate type culture apparatus or other apparatus which applies only a shear stress thereto. It is believed that at least the group of shear stress-responsive genes not modified by a normal stress act protectively against arteriosclerosis, and this gene group includes a gene and protein having an apoptosis-suppressing activity.

[0250] The endogenous transcription level of the DNA of the present invention having an apoptosis-suppressing activity, or the expression level of the protein of the present invention having an apoptosis-suppressing activity, or a structural change of the expressed protein may be detected using the DNA of the present invention having an apoptosis-suppressing activity, a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence of the DNA, an antibody capable of recognizing the protein of the present invention having an apoptosis-suppressing activity, or the like. Thus, the apoptosis sensitivity of cells can be identified.

[0251] Examples of the DNA used in the method for identifying apoptosis sensitivity, and an antibody capable of recognizing a protein encoded by the DNA include a DNA having the nucleotide sequence represented by SEQ ID NO:7, a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7, and an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.

[0252] The DNA of the present invention, a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence of the DNA, and an antibody capable of recognizing the protein of the present invention having an apoptosis-suppressing activity, which are used in the above-described method, are effective as agents for identifying the apoptosis sensitivity of cells.

[0253] Since the apoptosis of vascular endothelial cells is promoted in an arteriosclerotic lesion, these agents can also be utilized as diagnostic agents for vascular diseases caused by arteriosclerosis with a view, for example, to identifying the arteriosclerotic lesion or predicting the risk of developing arteriosclerosis in the future.

[0254] The agent for identifying the apoptosis sensitivity of cells include, for example, an agent containing a DNA having the nucleotide sequence represented by SEQ ID NO:7, a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7, an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8, or the like.

[0255] Since the DNAs of the present invention were obtained from human umbilical vein endothelial cells (HUVECs) as shear stress-responsive DNAs, it is desirable that the objective cells used for the identification of apoptosis sensitivity are vascular endothelial cells such as human primary cultured vascular endothelial cells and human umbilical vein endothelial cells (HUVECs). However, since apoptosis is a phenomenon universally observed in all types of cells of the living body including vascular endothelial cells, the objective cells are not limited to vascular endothelial cells.

(2) Regulation of the apoptosis of cells

[0256] Since the DNA of the present invention is a shear stress-responsive gene which is known to exhibit an increase of expression in response to a shear stress and lead to the suppression of apoptosis, the DNA of the present invention or a DNA having the same sequence as 5 to 60 consecutive bases in the DNA may be involved in the suppression of apoptosis. On the other hand, when an antisense DNA having a nucleotide sequence complementary to the nucleotide sequence of each of these DNAs is used, the apoptosis of cells is promoted because the endogenous transcription or translation of the DNA is suppressed.

[0257] Similarly to the DNA of the present invention, the apoptosis of cells may also be regulated using a protein encoded by the DNA of the present invention or an antibody capable of recognizing the protein. Specifically, a protein having an apoptosis-suppressing activity is selected from various proteins encoded by the DNAs of the present invention, and the DNA encoding this protein is integrated into a virus vector to create a recombinant virus vector. Then, the apoptosis of cells or a tissue may be suppressed by introducing the recombinant virus vector into the cells or tissue and expressing the protein having an apoptosis-suppressing activity.

[0258] Moreover, the apoptosis of cells may be regulated by using an antibody capable of recognizing the aforesaid protein and thereby giving a positive or negative apoptosis-regulating signal to the cells.

[0259] Examples of the method for suppressing or promoting apoptosis include a method for promoting the apoptosis of cells by suppressing the endogenous transcription or translation of the DNA using a DNA having the nucleotide sequence represented by SEQ ID NO:7, a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7, or an antisense DNA having a nucleotide sequence complementary to the nucleotide sequence of each of these DNAs, for example, according to the antisense technique; and a method for suppressing the apoptosis of cells by introducing the DNA into the cells and thereby accelerating the transcription of the DNA.

[0260] Moreover, they also include a method for suppressing the apoptosis of cells by increasing the intracellular expression level of a protein having the amino acid sequence represented by SEQ ID NO:8, using a recombinant virus vector containing a DNA having the nucleotide sequence represented by SEQ ID NO:7, a recombinant virus vector

containing an RNA comprising a sequence homologous with the sense strand of the DNA having the nucleotide sequence represented by SEQ ID NO:7, or a recombinant virus vector capable of producing a protein having the amino acid sequence represented by SEQ ID NO:8.

[0261] Furthermore, since the amino acid sequence represented by SEQ ID NO:8 is considered to be a membrane protein on the basis of its structure, they also include a method for regulating the apoptosis of cells by subjecting the cells to the action of an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8, stimulating the protein expressed on the cell surface, and thereby transducing a positive or negative apoptosis-regulating signal in the cells.

[0262] The DNA of the present invention, a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence of the DNA, a recombinant virus vector capable of expressing the protein of the present invention having an apoptosis-suppressing activity, and an antibody capable of recognizing the protein of the present invention, which are used in the above-described methods, are effective as agents for regulating the apoptosis of cells. These agents can also be utilized as therapeutic agents for vascular diseases caused by arteriosclerosis.

[0263] The agents for regulating apoptosis include, for example, an agent containing a DNA having the nucleotide sequence represented by SEQ ID NO:7, a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7, an antisense DNA having a nucleotide sequence complementary to the nucleotide sequence of each of these DNAs, a recombinant virus vector containing a DNA having the nucleotide sequence represented by SEQ ID NO:7, a recombinant virus vector containing an RNA comprising a sequence homologous with the sense strand of the DNA having the nucleotide sequence represented by SEQ ID NO:7, a recombinant virus vector capable of producing a protein having the amino acid sequence represented by SEQ ID NO:8, or an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.

[0264] Since the DNAs of the present invention were obtained from human umbilical vein endothelial cells (HUVECs) as shear stress-responsive DNAs, it is desirable that the objective cells used for the regulation of apoptosis are vascular endothelial cells such as human primary cultured vascular endothelial cells and human umbilical vein endothelial cells (HUVECs). However, since apoptosis is a phenomenon universally observed in all types of cells of the living body including vascular endothelial cells, the objective cells are not limited to vascular endothelial cells.

(3) Screening of an agent for regulating the apoptosis of cells

[0265] The methods for screening an agent for regulating the apoptosis of cells using the shear stress-responsive DNA of the present invention or a protein encoded by the DNA are described below.

[0266] One of the aforesaid screening methods is such that, when apoptosis is induced in an animal cell line exhibiting the Fas-dependent induction of apoptosis, a compound or protein which can suppress or promote apoptosis by regulating the endogenous transcription or translation of the DNA of the present invention is selected.

[0267] In particular, a compound or protein which can suppress apoptosis by promoting the endogenous transcription or translation of the DNA of the present invention is effective for the treatment of vascular diseases caused by arteriosclerosis. On the other hand, a compound or protein which can promote apoptosis by suppressing the endogenous transcription or translation of the DNA of the present invention is effective for the treatment of diseases based on abnormal proliferation of cells, such as cancer.

[0268] According to one exemplary method for screening an agent for regulating the apoptosis of cells using the DNA of the present invention, after a test material is made to act on cells, an increase or decrease of the endogenous transcription level of a DNA having the nucleotide sequence represented by SEQ ID NO:7 is assayed using the DNA having the nucleotide sequence represented by SEQ ID NO:7, or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7. Thus, an agent for suppressing or promoting the apoptosis of the cells can be screened.

[0269] Another of the aforesaid screening methods is such that, when an animal cell which has been transformed by introducing the DNA of the present invention so as to produce the protein of the present invention or a partial polypeptide of the protein is used, a compound or protein which can suppress the apoptosis of the cell by binding specifically to the cell is selected. In this method, the specific binding of a compound or protein can be detected by using an untransformed cell as a control. The agent obtained by this screening is also effective for the treatment of vascular diseases caused by arteriosclerosis.

[0270] According to one exemplary screening method using the protein of the present invention, a DNA having the nucleotide sequence represented by SEQ ID NO:7 is introduced into cells using a recombinant virus vector containing the DNA having the nucleotide sequence represented by SEQ ID NO:7, or a recombinant virus vector containing an RNA comprising a sequence homologous with the sense strand of the DNA having the nucleotide sequence represented by SEQ ID NO:7, to express a protein having the amino acid sequence represented by SEQ ID NO:8. By exposing the cells to a test material so as to contact the test material with the protein, an agent which binds specifically to the protein to change the activity of the protein is selected. Thus, an agent for suppressing or promoting the apoptosis

of cells can be screened.

[0271] Alternatively, a DNA having the nucleotide sequence represented by SEQ ID NO:7 or a DNA encoding a protein having the amino acid sequence represented by SEQ ID NO:8 is inserted into a vector to construct a recombinant DNA. This recombinant DNA is introduced into a host cell, and the resulting transformant is cultured in a culture medium. By using the resulting culture to contact the protein in the culture with a test material, an agent which binds specifically to the protein to change the activity of the protein is selected. Thus, an agent for suppressing or promoting the apoptosis of cells can be screened.

[0272] Alternatively, an isolated and purified protein having the amino acid sequence represented by SEQ ID NO:8 or a partial peptide of the protein having the amino acid sequence represented by SEQ ID NO:8 is used in an *in vitro* system. By contacting a test material with the protein or the peptide, an agent which binds specifically to the protein or peptide to cause a change in the activity of the protein is selected. Thus, an agent for suppressing or promoting the apoptosis of cells can be screened.

[0273] When an agent for suppressing or promoting apoptosis is screened by using an increase or decrease of the transcription level of a DNA having the nucleotide sequence represented by SEQ ID NO:7 in the cells as an index, the transcription level of the DNA may be analyzed according to a technique such as Northern hybridization, *in situ* hybridization, RNase protection assay or RT-PCR, by using a probe or primer comprising the DNA having the nucleotide sequence represented by SEQ ID NO:7, or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7.

[0274] When an agent for suppressing or promoting apoptosis is screened by using the expression level of a protein having the amino acid sequence represented by SEQ ID NO:8 in the cells as an index, the expression level of the protein may be analyzed according to an immunological detection technique using an antibody capable of recognizing the protein having the amino acid sequence represented by SEQ ID NO:8.

[0275] The agents obtained by the above-described screening methods can be utilized as an agent for suppressing or promoting the apoptosis of cells.

[0276] Since the DNAs of the present invention were obtained from human umbilical vein endothelial cells (HUVECs) as shear stress-responsive DNAs, it is desirable that the objective cells used for the regulation of apoptosis are vascular endothelial cells such as human primary cultured vascular endothelial cells and human umbilical vein endothelial cells (HUVECs). However, since apoptosis is a phenomenon universally observed in all types of cells of the living body including vascular endothelial cells, the objective cells are not limited to vascular endothelial cells.

[0277] As the vector used to express the DNA of the present invention in an animal cell and the method for introducing a recombinant vector, there may be employed any of the previously described methods.

[0278] As the immunological detection technique for assaying an increase or decrease of the expression level of the protein of the present invention using an antibody, there may be employed any of the previously described techniques.

[0279] As the host cell required in a screening system for detecting the suppression or promotion of apoptosis, there may be used any animal cell that exhibits the Fas-dependent induction of apoptosis. Examples thereof include suspension type cells such as Jurkat [J. Exp. Med., 152, 1709-19(1980)], HPB-ALL [Int. J. Cancer, 21, 166-170(1978)] and SKW6.4 [Immunol. Lett., 7, 17-23(1983)]; and adhesion type cells such as HeLa and A673 [Arch. Biochem. Biophys., 230, 93-102(1984)].

[0280] One example of a substance for inducing Fas-dependent cell death in the aforesaid cell lines is the anti-human Fas monoclonal antibody CH-11 [J. Exp. Med., 169, 1747-1756(1989)]. Exemplary methods for inducing cell death are as follows. In the case of a suspension type cell, a cell suspension is diluted with a culture medium so as to have a density of about 10^6 cells/ml and added to a 24-well plate or a 96-well microtiter plate for the culture of animal cells. After the anti-human Fas monoclonal antibody is added to a concentration of 1 to 500 ng/ml, the plate is incubated in a CO₂ incubator at 37°C for several hours to 2 day and culture is carried out. In the case of an adhesion type cell, cells are inoculated onto a plate in advance. When cell death is to be induced, the culture medium is replaced by a culture medium containing the anti-human Fas monoclonal antibody, and the culture is continued in a CO₂ incubator at 37°C.

[0281] As the method for detecting the suppression or promotion of apoptosis, there may be employed, for example, a detection method in which the cells are stained with trypan blue, Giemsa stain or the like and observed under an optical microscope. In the case of adhesion type cells, apoptosis causes cells to detach from the plate and float. Accordingly, the occurrence of apoptosis can be easily detected without staining. Also known is a detection method in which the cells are stained with a fluorochrome such as Hoechst 33342, Hoechst 33258 or propidium iodide and observed under a fluorescence microscope [Biomaterial UP Series, New Experimental Methods for the Research of Apoptosis (in Japanese), Second Edition]. Moreover, there may also be employed biochemical methods such as a method involving the measurement of the activity of caspase activated in the process of apoptosis [J. Exp. Med., 183, 1957-1964 (1996)], and MTT assay involving the measurement of mitochondrial dehydrogenase activity in living cells [J. Immunol. Methods, 16, 55-63(1983)]. Furthermore, a method for detecting a structural change of cell membrane using Annexin V [J. Exp. Med., 182, 1545-1556(1995)], and detection methods based on DNA fragmentation such as TUNEL method

and Burton's method [Biomannual UP Series, New Experimental Methods for the Research of Apoptosis (in Japanese), Second Edition] are also known.

Examples

[0282] The present invention is more specifically described hereinbelow with reference to the following examples. However, the present invention is in no way to be limited to these examples.

Example 1

Construction of a cDNA library from HUVECs having a shear stress applied thereto

(1) Culture of HUVECs

[0283] Using F-12K medium (manufactured by Dainippon Pharmaceutical Co., Ltd.) containing 10% fetal calf serum, 1% penicillin (5,000 units/ml)/streptomycin (5 mg/ml) solution (manufactured by Life Technologies), 0.003% Endothelial Cell Growth Supplement (manufactured by Becton Dickinson), 0.01% heparin (manufactured by Wako Pure Chemical Industries Ltd.) and 0.14% NaHCO_3 (manufactured by Life Technologies), HUVECs were cultured and subcultured under the condition of 5% CO_2 and 37°C. The HUVECs used were purchased from Clonetics.

(2) Application of a shear stress to HUVECs

[0284] A suspension of 0.2 g of micro-carriers (Cytodex 3; manufactured by Amersham Pharmacia Biotech) in 10 ml of PBS buffer was transferred to a sterilized 50 ml tube, and centrifuged at 1,000 rpm for 3 minutes at room temperature. After the supernatant was removed, F12K medium was added. After the resulting suspension was centrifuged again and the supernatant was removed, the medium was added to make up to about 10 ml.

[0285] After the HUVECs obtained in the above culture step (1) were dissociated with trypsin/EDTA, about 2×10^6 HUVECs were suspended in 10 ml of the medium and mixed with the above-described micro-carriers. This mixture was transferred to a 200 ml spinner flask, and 15 ml of the medium was added to make a total volume of about 35 ml. The mixture was stirred at 50-60 rpm for 30 seconds and then allowed to stand for one hour. By repeating this stirring/standing procedure four times, HUVECs were made to adhere to the micro-carriers. Thereafter, a shear stress was applied to the cells by stirring the mixture at 160 rpm for a selected period of time.

(3) Preparation of RNA

[0286] Samples of 1.6×10^7 HUVECs having a shear stress applied thereto for 0.5 hour, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 6 hours, 10 hours, and 20 hours respectively were prepared in the manner described in the above step (2). From each of the aforesaid nine samples of cells having different shear stress application times, total RNAs were prepared by the guanidine thiocyanate-caesium trifluoroacetate method [Methods in Enzymology, 154, 3(1987)]. 100 μg each of these total RNAs from the nine samples were mixed to obtain 900 μg of total RNA. This 900 μg of total RNA was passed through an oligo-dT cellulose column (manufactured by Collaborative Research) to obtain 30.9 μg of mRNA as poly(A)⁺ RNA.

(4) Construction of a cDNA library

[0287] Using 3.0 μg of mRNA obtained in the above step (3), the synthesis of cDNA, the addition of BamHI adapter, and cleavage reaction with NotI were carried out according to the linker primer method [Hiroshi Nojima ed., "Methods for the Construction of Gene Libraries" (in Japanese)]. The resulting double-stranded cDNAs were ligated between BglII/NotI of the plasmid vector pAP3neo [Genes to Cells, 3, 459(1998)] so that 5'-terminus of the cDNAs was always located on the BglII site of the vector. Using the resulting ligation reaction solution, the plasmid was introduced into *Escherichia coli* MC1061A (Molecular Cloning, Second Edition) by electroporation. Thus, a cDNA library was constructed.

Example 2Construction of a subtraction library

5 (1) Preparation of single-strand DNA

[0288] 2 µg of the plasmid of the cDNA library obtained in Example 1 by amplification in MC1061A was introduced into *Escherichia coli* XL1-Blue MRF⁺ (manufactured by Stratagene) by electroporation. After this *Escherichia coli* was suspended in 4.5 ml of SOC medium (Molecular Cloning, Second Edition) and incubated at 37°C for 1 hour with vigorous shaking, all of the resulting culture was added to 5.5 ml of LB medium (Molecular Cloning, Second Edition) containing 50 µg/ml ampicillin. After being incubated at 37°C for 5 hours with vigorous shaking, 5 ml of the resulting culture was inoculated into 45 ml of 2-YT medium (Molecular Cloning, Second Edition) containing ampicillin, and 1 x 10¹¹ pfu of helper phage R408 [Gene, 45, 333(1986)] was added thereto. After being incubated at 37°C for 12 hours with vigorous shaking, the resulting culture was transferred to a sterilized tube and centrifuged at 10,000 rpm for 10 minutes at 4°C to precipitate the *Escherichia coli*. The phage-containing supernatant was transferred to a new sterilized tube and centrifuged again. The supernatant was passed through a sterilizing filter (manufactured by Millipore) having a pore diameter of 0.22 µm to remove the *Escherichia coli* completely. 2.5 ml of 10-DNase buffer [100 mM Tris-HCl (pH 7.5), 100 mM MgCl₂], 1 µl of 20 units/µl DNase I (manufactured by Nippon Gene Co., Ltd.) were added to 25 ml of the phage solution, and this mixture was reacted at 37°C for 30 minutes. Then, 1/4 volume of 20% polyethylene glycol (molecular weight 6,000)/2.5 M NaCl was added thereto and mixed well, following by standing at room temperature for 20 minutes. After this mixture was centrifuged at 10,000 rpm for 10 minutes at 4°C, the supernatant was removed completely. The resulting precipitate of phage was dissolved in 400 µl of TE [10 mM Tris-HCl (pH 8.0), 1 mM EDTA (pH 8.0)], and 25 µl of 25 mg/ml Proteinase K and 4 µl of 10% SDS were added thereto, following by reaction at 42°C for 1 hour. The reaction mixture was subjected to a phenol treatment, a phenol-chloroform treatment and a chloroform treatment, and then precipitated with ethanol. The resulting precipitate of single-strand phage DNA was dissolved in 30 µl of TE.

(2) Biotinylation of RNA

[0289] In the same manner as in Example 1, poly(A)⁺ RNA was prepared from HUVECs having no shear stress applied thereto (i.e., HUVECs made only to adhere to micro carriers). To 30 µg of this RNA was added distilled water so as to make a volume of 20 µl. Then, 30 µl of 1 µg/µl PHOTOPROBE blotIn (manufactured by Vector Laboratories) was added thereto in the dark. After the tube was uncapped and placed on ice, the mixture was irradiated with light from a mercury vapor lamp disposed about 10 cm above the tube for 20 minutes to biotinylate the RNA, followed by the addition of 50 µl of 100 mM Tris-HCl (pH 9.5)/1 mM EDTA (pH 8.0). Then, 100 µl of water-saturated butanol was added thereto, followed by vigorous stirring. After this mixture was centrifuged at 14,000 rpm for 5 minutes at 4°C, the upper butanol layer was removed. This procedure was repeated two more times. 100 µl of chloroform was added to the aqueous layer, followed by vigorous stirring. After this mixture was centrifuged at 14,000 rpm for 5 minutes at 4°C, the aqueous layer was transferred to a new tube. After this procedure was repeated again, RNA was precipitated with ethanol. The recovered precipitate of RNA was dissolved in 20 µl of distilled water, and subjected again to the procedure for biotinylation. The biotinylated RNA was preserved at -80°C in the ethanol-precipitated state till use for hybridization.

(3) Hybridization of single-strand DNA with RNA

[0290] 20 µg of the biotinylated RNA prepared in step (2) was recovered by centrifugation at 14,000 rpm for 15 minutes at 4°C, and dissolved in 8 µl of distilled water. To this solution, 12.5 µl of 2 x reaction buffer [80% formamide, 100 mM HEPES (pH 7.5), 2 mM EDTA (pH 8.0), 0.2% SDS], 2.5 µl of 2.5 M NaCl, 1 µl of 1 µg/µl poly(A) (manufactured by Amersham Pharmacia Biotech), and 1 µl (0.5 µg/µl) of the single-strand DNA prepared in step (1) from the cDNA library derived from HUVECs having a shear stress applied thereto were added so as to make a total volume of 25 µl. After this mixture was heated at 65°C for 10 minutes, it was quickly transferred to a heat block warmed at 42°C and incubated at 42°C for two nights to effect hybridization.

(4) Subtraction and rehybridization

[0291] After completion of the hybridization, 400 µl of a buffer [500 mM NaCl, 50 mM HEPES (pH 7.5), 2 mM EDTA (pH 8.0)] was added to the reaction mixture. Then, 5 µl of 2 µg/µl streptavidin (manufactured by Life Technologies) was added thereto and mixed therewith. After this mixture was allowed to stand at room temperature for 5 minutes, it was subjected to a phenol-chloroform treatment. The aqueous layer was transferred to a new tube, and 5 µl of fresh

streptavidin was added thereto. After this mixture was allowed to stand at room temperature for 5 minutes, subtraction was carried out by subjecting it twice to a phenol-chloroform treatment and once to a chloroform treatment. The aqueous layer was placed in the upper chamber of a Millipore Filter UFCP3TK50 (manufactured by Millipore) and centrifuged at 10,000 rpm at 4°C until all of the solution passed into the lower chamber. After the solution was removed from the lower chamber, the filter was washed by adding 300 µl of TE to the upper chamber and centrifuging the filter. After this procedure was repeated, single-strand DNA captured on the filter was recovered with 30 µl of 1/10 TE. This single-strand DNA was dried under vacuum and dissolved in distilled water to make up to 9 µl. After 10 µg of the biotinylated RNA prepared in step (2) was precipitated with ethanol and recovered by centrifugation, 9 µl of the above single-strand DNA solution was added to the precipitate. After the addition of 12.5 µl of 2 x reaction buffer, 2.5 µl of 2.5 M NaCl, and 1 µl of poly(A), a second hybridization step was carried out in the same manner as in step (3), and subtraction was carried out in the above-described manner. Thereafter, single-strand DNA was recovered in a similar manner and subjected to a third subtraction step by hybridization with 10 µg of the biotinylated RNA and a fourth subtraction step by using 5 µg of the biotinylated RNA.

(5) Synthesis of double-strand DNA and its introduction into Escherichia coli

[0292] After four subtraction steps were successively carried out as described above, the resulting single-strand DNA was recovered in 30 µl of 1/10 TE. To a 15 µl portion thereof, 14 µl of distilled water and 1 µl of a 2 µg/µl primer extension primer having the nucleotide sequence represented by SEQ ID NO: 159 were added, followed by heating at 65°C for 10 minutes. After this mixture was allowed to stand at room temperature for 5 minutes so as to anneal the primer to single-strand DNA, 5 µl of 10 x reaction buffer (attached to BcaBEST Dideoxy Sequencing Kit; manufactured by Takara Shuzo Co., Ltd.), 10 µl of a 1 mM dNTP mixture, 0.5 µl of 3 µg/µl single-strand DNA-binding protein (manufactured by USB), 2 µl of 2 units/µl BcaBEST DNA polymerase (manufactured by Takara Shuzo Co., Ltd.), and 2.5 µl of distilled water were added thereto. This mixture was reacted at 65°C for 1 hour to synthesize double-strand DNA. After the addition of 50 µl of distilled water, the reaction mixture was subjected to a phenol-chloroform treatment and a chloroform treatment. The resulting solution was concentrated by means of a Millipore Filter UFCP3TK50, and the double-strand DNA was finally dissolved in 20 µl of TE. Using 1/5 volume of this solution, the double-strand DNA was introduced into Escherichia coli MC1061A by electroporation.

(6) Reverse subtraction

[0293] Escherichia coli MC1061A having the double-strand DNA introduced thereto, which was obtained in step (5), was cultured, and plasmid DNA was prepared from the Escherichia coli. In the same manner as in step (1), this plasmid DNA was introduced into Escherichia coli XL1-Blue MRF' to prepare single-strand DNA. Two µg of mRNA derived from HUVECs having a shear stress applied thereto was biotinylated in the manner described in step (2), and mixed with 2 µg of the aforesaid single-strand DNA. To this mixture, 12.5 µl of 2 x reaction buffer, 2.5 µl of 2.5 M NaCl, 1 µl of 1 µg/µl poly(A), and 1 µl of distilled water were added so as to make a total volume of 25 µl. In the same manner as in step (3), this mixture was incubated at 42°C for two nights to carry out hybridization. Four hundred µl of a buffer [500 mM NaCl, 50 mM HEPES (pH 7.5), 2 mM EDTA (pH 8.0)] was added to the reaction mixture. Then, 7 µl of 2 µg/µl streptavidin was added thereto and mixed therewith. After this mixture was allowed to stand at room temperature for 5 minutes, phenol-chloroform was added thereto with vigorous mixing. After this mixture was centrifuged at 14,000 rpm for 7 minutes at room temperature, the aqueous layer was removed. Then, 400 µl of fresh TE was added thereto with vigorous mixing. After this mixture was centrifuged at 14,000 rpm for 7 minutes at room temperature, the aqueous layer was removed. This procedure was repeated two more times, so that single-strand DNA which did not hybridize with the biotinylated RNA was removed. After 400 µl of TE was added without mixing, the tube was heated at 95°C for 5 minutes in the uncapped state. Thereafter, by placing the tube on ice for 5 minutes to denature the DNA, the single-strand DNA having hybridized with the biotinylated RNA and present in the phenol-chloroform layer was separated from the biotinylated RNA. After the reaction mixture was vigorously mixed and centrifuged at 14,000 rpm for 7 minutes at room temperature, the aqueous layer was transferred to a new tube. The aqueous layer was subjected again to a phenol-chloroform treatment and then to a chloroform treatment. The aqueous layer containing the single-strand DNA was concentrated by means of a Millipore Filter UFCP3TK50, and the single-strand DNA was finally recovered in 30 µl of 1/10 TE. Fifteen µl of this solution was dried under vacuum, and dissolved in distilled water to make up to 9 µl. Five µg of mRNA derived from HUVECs having no shear stress applied thereto was biotinylated and recovered by precipitation with ethanol. To the precipitate was added 9 µl of the aforesaid single-strand DNA solution. Then, 12.5 µl of 2 x reaction buffer, 2.5 µl of 2.5 M NaCl, and 1 µl of poly(A) were added thereto, and normal subtraction was carried out in the same manner as steps (3) and (4).

[0294] That is, a subtraction library in which genes exhibiting an increase of expression in response to the application of a shear stress in HUVECs were concentrated was prepared by carrying out four successive subtraction steps, one

reverse subtraction step, and one normal subtraction step.

Example 3

Obtaining of clones exhibiting an alteration of expression by Northern hybridization

[0295] Northern hybridization was carried out in order to select clones which are included in the subtraction library obtained in Example 2 and exhibit a shear stress-dependent increase of expression.

(1) Transfer of RNA to a membrane

[0296] According to the same procedure as in Example 1, total RNAs were obtained from HUVECs having a shear stress applied thereto and HUVECs having no shear stress applied thereto, respectively. To 4 µg of each total RNA was added distilled water so as to make a volume of 1.8 µl. Then, 0.8 µl of 10 x MOPS buffer [80 mM sodium acetate, 197 mM MOPS, 10 mM EDTA (pH 8.0)], 1.4 µl of a 35% formaldehyde solution (manufactured by Nacalai Tesque), and 4 µl of deionized formamide were added thereto. After this mixture was heated at 65°C for 15 minutes and then cooled rapidly by placing it on ice for 5 minutes, the total amount thereof was electrophoresed through 1 x MOPS/2% formaldehyde/1% agarose gel. After completion of the electrophoresis, the gel was washed with distilled water for 20 minutes, and this washing step was repeated three times to remove any formaldehyde from the gel. After the gel was soaked in 20xSSC (3 M NaCl, 0.3 M sodium citrate) for 30 minutes, RNA in the gel was transferred to a nylon membrane Biodyne A (manufactured by Pall BioSupport) according to a capillary transfer method using 20xSSC. After completion of the transfer, the RNA was fixed to the membrane by allowing the membrane to stand at 80°C for 2 hours.

(2) Labeling of probes

[0297] In the subtraction library obtained in Example 2, clones having an inserted DNA fragment of not less than 0.4 kb size were treated by cleaving the plasmid with SmaI and NotI to excise the inserted DNA fragment. The fragments thus obtained were purified using a QIAquick Gel Extraction Kit (manufactured by QIAGEN), and the procedure therefor was carried out according to the manual attached to the kit. Using about 50 ng of the purified DNA fragments as templates, the DNA fragments were labeled using a Random Primer DNA Labelling Kit Ver. 2 (manufactured by Takara Shuzo Co., Ltd.) and [α -³²P]dCTP (110 TBq/mmol; Amersham Pharmacia Biotech), and used as probes. The procedure therefor was carried out according to the manual attached to the kit.

(3) Hybridization and autoradiography

[0298] The membrane prepared in step (1) was placed in a hybridization bag, and a freshly prepared hybridization solution [50% formamide, 5 x Denhardt's, 5 x SSC, 0.1% SDS, denatured salmon DNA (0.1 mg/ml)] was added thereto. The hybridization bag was incubated at 42°C for 2 hours or more to carry out prehybridization. The probes prepared in step (2) were denatured by heating them at 95°C for 5 minutes and cooling them rapidly. These probes were mixed with a hybridization solution and added to the prehybridized membrane. The hybridization bag was incubated at 42°C for 24 hours or more to carry out hybridization. The membrane was taken out of the hybridization bag, placed in 2 x SSC/0.1% SDS, and slowly shaken at room temperature for 10 minutes to remove the hybridization solution as much as possible. Then, the membrane was washed in 0.15 x SSC/0.1% SDS at 42°C for 30 minutes, and this washing step was repeated twice. After completion of the washing steps, autoradiography was carried out by exposing an X-ray film to the membrane. A total of 1,026 clones were named A4RS-1 to A4RS-1026, respectively, and each of them was subjected to Northern hybridization. Thus, there were obtained 107 clones exhibiting a shear stress-dependent increase of expression.

Example 4

Identification of clones exhibiting alteration of expression

(1) Determination of nucleotide sequences

[0299] With respect to the clones which were ascertained to exhibit an increase of expression in response to the application of a shear stress in Example 3, their nucleotide sequences were determined by means of a 377 DNA Sequencer (manufactured by Perkin Elmer). For the determination of the nucleotide sequences, a Dye Primer Cycle Sequencing Kit (manufactured by Perkin Elmer) was used. The procedure therefor was carried out according to the

attached manual. The clones exhibiting alteration of expression were identified by comparing the resulting nucleotide sequences with the database GenBank. As a result, the 107 clones were classified into 88 types of genes. In these 88 genes, 5 genes which have been reported to exhibit the induction of expression by a shear stress stimulus in vascular endothelial cells, i.e. the genes encoding endothelin 1, monocyte chemotactic protein 1, heparin-binding EGF-like growth factor, thrombomodulin, and transforming growth factor β , are included. Accordingly, 83 genes with which the induction of expression by a shear stress stimulus in vascular endothelial cells had not yet been reported could be identified. These genes included 55 known genes and 28 novel genes. With respect to genes whose sequences are not identical with any of the full-length cDNAs included in the known sequences, but are identical only with expressed sequence tags (ESTs) alone, and genes whose sequences are not identical with any of the known sequences (i.e., novel genes), all ESTs included in the corresponding UniGene are joined together to construct as long sequences as possible on a computer. With respect to eight of the novel genes, full-length cDNAs were cloned from a cDNA library prepared with a λ phage vector in Example 5 that will be given later.

(2) Known genes exhibiting a shear stress-dependent increase of expression

[0300] When the nucleotide sequence of A4RS-016 was determined, this was identical with the sequence of thioredoxin reductase [Accession: X91247] (SEQ ID NO:1). The amino acid sequence encoded by this gene is shown as SEQ ID NO:2. Thioredoxin reductase is an enzyme reducing thioredoxin using NADPH, and participates in various physiological reactions such as control of intracellular antioxidation, signal transduction, and NO production. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 1 of FIG. 1 and lane 1 of FIG. 3.

[0301] When the nucleotide sequence of A4RS-026 was determined, this was identical with the sequence of lipopolysaccharide-induced protein gene [Accession: Q51544] (SEQ ID NO:3). The amino acid sequence encoded by this gene is shown as SEQ ID NO:4. The protein encoded by this gene does not show substantial homology with other known proteins, and its function is unknown. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 2 of FIG. 1.

[0302] When the nucleotide sequence of A4RS-040 was determined, this was identical with the sequence of spliceosome-associated protein (SAP145) [Accession: U41371] (SEQ ID NO:5). The amino acid sequence encoded by this gene is shown as SEQ ID NO:6. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 3 of FIG. 1.

[0303] When the nucleotide sequence of A4RS-041 was determined, this was identical with the sequence of human proline-rich membrane protein (PRMP) [Accession: V50494] (SEQ ID NO:7). The amino acid sequence encoded by this gene is shown as SEQ ID NO:8. Only the sequence of PRMP is registered in a database, and its function is unknown. However, PRMP has substantial homology with rat neural membrane protein 35 (NMP35) [Molecular and Cellular Neuroscience, 11, 260(1998)] and the glutamate-binding subunit of NMDA receptor [Accession: W62612]. Although the function of NMP35 is not clearly known, it is expressed specifically in the brain, like the glutamate-binding subunit of NMDA receptor. From an analysis of hydrophilicity on the basis of its amino acid sequence, NMP35 is presumed to be a membrane protein. PRMP also has an extremely high degree of hydrophobicity and hence functions as a membrane protein. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 4 of FIG. 1 and lane 2 of FIG. 3.

[0304] When the nucleotide sequence of A4RS-063 was determined, this was identical with the sequence of puromycin-sensitive aminopeptidase [Accession: AJ132583] (SEQ ID NO:9). The amino acid sequence encoded by this gene is shown as SEQ ID NO: 10. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 5 of FIG. 1 and lane 3 of FIG. 3.

[0305] When the nucleotide sequence of A4RS-096 was determined, this was identical with the sequence of human secreted protein gene 125 clone HSPAG15 [Accession: V59635] (SEQ ID NO:11). The amino acid sequence encoded by this gene is shown as SEQ ID NO:12. Only the sequence of this gene is registered in a bank, and its function is unknown. The protein encoded by this gene does not show substantial homology with other known proteins. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 6 of FIG. 1 and lane 4 of FIG. 3.

[0306] When the nucleotide sequence of A4RS-116 was determined, this was identical with the sequence of lamin C [Accession: M13451] (SEQ ID NO:13). The amino acid sequence encoded by this gene is shown as SEQ ID NO: 14. Lamin C is a lining protein for the nuclear membrane and is one of the cytoskeleton forming factors. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 7 of FIG. 1 and lane 5 of FIG. 3.

[0307] When the nucleotide sequence of A4RS-126 was determined, this was identical with the sequence of cytokine-response gene CR8 [Accession: T43383] (SEQ ID NO:15). The amino acid sequence encoded by this gene is shown as SEQ ID NO:16. Cytokine-response gene CR8, which is also called DEC1, is a transcription factor having a basic helix-loop-helix motif. In particular, it has high homology with a HES family of transcription factors participating in nerve differentiation. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 8 of FIG. 1.

[0308] When the nucleotide sequence of A4RS-131 was determined, this was identical with the sequence of human

enhancer of filamentation (HEF1) [Accession: L43821] (SEQ ID NO:17). The amino acid sequence encoded by this gene is shown as SEQ ID NO:18. HEF1 is a signal transduction molecule having an SH3 domain, having a FAK-binding activity, and participating in regulation of the cytoskeleton. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 9 of FIG. 1.

5 [0309] When the nucleotide sequence of A4RS-148 was determined, this was identical with the sequence of interferon-induced 15-kDa protein gene [Accession: M21786] (SEQ ID NO:19). The amino acid sequence encoded by this gene is shown as SEQ ID NO:20. The protein encoded by this gene does not show substantial homology with other known proteins, and its function is unknown. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 10 of FIG. 1.

10 [0310] When the nucleotide sequence of A4RS-154 was determined, this was identical with the sequence of LDL receptor [Accession: N60388] (SEQ ID NO:21). The amino acid sequence encoded by this gene is shown as SEQ ID NO:22. LDL receptor incorporates LDL, which is one of the causes for the formation of an arteriosclerotic lesion, under the endothelium. It has been reported that, when a shear stress is applied to cultured bovine aortic endothelial cells, the binding and incorporation of LDL via LDL receptor increases [Circulation; 76, 648(1987)]. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 11 of FIG. 1.

15 [0311] When the nucleotide sequence of A4RS-174 was determined, this was identical with the sequence of peripheral myelin protein (PMP)-22 [Accession: Q32869] (SEQ ID NO:23). The amino acid sequence encoded by this gene is shown as SEQ ID NO:24. PMP-22 is a component of myelin present in the peripheral nervous system, and is a membrane protein having four transmembrane domains. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 12 of FIG. 1.

20 [0312] When the nucleotide sequence of A4RS-175 was determined, this was identical with the sequence of tyrosine kinase receptor UFO/Ark [Accession: S65125] (SEQ ID NO:25). The amino acid sequence encoded by this gene is shown as SEQ ID NO:26. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 13 of FIG. 1.

25 [0313] When the nucleotide sequence of A4RS-194 was determined, this was identical with the sequence of calcium-ATPase HK2 [Accession: M23115] (SEQ ID NO:27). The amino acid sequence encoded by this gene is shown as SEQ ID NO:28. Calcium-ATPase HK2 is present in the membranes of the endoplasmic reticulum within cells. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 14 of FIG. 1.

30 [0314] When the nucleotide sequence of A4RS-197 was determined, this was identical with the sequence of human arginine-rich protein [Accession: M83751] (SEQ ID NO:29). The amino acid sequence encoded by this gene is shown as SEQ ID NO:30. The amino acid sequence encoded by this gene does not show substantial homology with other known proteins, and its function is unknown. However, it is suggested that this gene may be a kind of proto-oncogene. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 15 of FIG. 1.

35 [0315] When the nucleotide sequence of A4RS-260 was determined, this was identical with the sequence of KIAA0025 [Accession: D14695] (SEQ ID NO:31). The amino acid sequence encoded by this gene is shown as SEQ ID NO:32. The protein encoded by this gene does not show substantial homology with other known proteins, and its function is unknown. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 16 of FIG. 1 and lane 6 of FIG. 3.

40 [0316] When the nucleotide sequence of A4RS-271 was determined, this was identical with the sequence of human high-mobility group phosphoprotein isoform I-C (HMGI-C) [Accession: U28749] (SEQ ID NO:33). The amino acid sequence encoded by this gene is shown as SEQ ID NO:34. Judging from its structure, HMGI-C is a transcription factor. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 17 of FIG. 1 and lane 7 of FIG. 3.

45 [0317] When the nucleotide sequence of A4RS-307 was determined, this was identical with the sequence of PRAD1 [Accession: X59798] (SEQ ID NO:35). The amino acid sequence encoded by this gene is shown as SEQ ID NO:36. PRAD1 is a member of the cyclin family and is also called cyclin D1. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 18 of FIG. 1 and lane 8 of FIG. 3.

50 [0318] When the nucleotide sequence of A4RS-355 was determined, this was identical with the sequence of KIAA0964 [Accession: AB023181] (SEQ ID NO:37). The amino acid sequence encoded by this gene is shown as SEQ ID NO:38. The protein encoded by this gene is judged to be the human ortholog of rat PSD-95/SAP90-associated protein-4 (SAPAP-4). SAPAP-4 is present in membranes and is considered to participate in the clustering of NMDA receptor. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 19 of FIG. 1.

55 [0319] When the nucleotide sequence of A4RS-389 was determined, this was identical with the sequence of lamin A [Accession: M13452] (SEQ ID NO:39). The amino acid sequence encoded by this gene is shown as SEQ ID NO:40. Lamin A is a lining protein for the nuclear membrane and is one of the cytoskeleton forming factors. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in panel 20 of FIG. 1 and panel 9 of FIG. 3.

[0320] When the nucleotide sequence of A4RS-391 was determined, this was identical with the sequence of non-muscle alpha actinin [Accession: U48734] (SEQ ID NO:41). The amino acid sequence encoded by this gene is shown

as SEQ ID NO:42. Alpha actinin is one of the cytoskeleton forming factors. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 21 of FIG. 1 and lane 10 of FIG. 3.

[0321] When the nucleotide sequence of A4RS-423 was determined, this was identical with the sequence of gamma-filamin [Accession: AF089841] (SEQ ID NO:43). The amino acid sequence encoded by this gene is shown as SEQ ID NO:44. Gamma-filamin is an actin filament crosslinking protein, and participates in filopodia formation by binding to low-molecular-weight GTP-binding proteins such as rac and rho. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 22 of FIG. 1.

[0322] When the nucleotide sequence of A4RS-431 was determined, this was identical with the sequence of growth factor inducible immediate early gene product CYR61 [Accession: U62015] (SEQ ID NO:45). The amino acid sequence encoded by this gene is shown as SEQ ID NO:46. CYR61 is also called glg1, monocyte mature differentiation factor, or connective tissue growth factor-2, and is a secreted factor having a signal sequence at the amino-terminus. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 23 of FIG. 1.

[0323] When the nucleotide sequence of A4RS-453 was determined, this was identical with the sequence of nuclear factor of activated T cells (NF-ATc) [Accession: U08015] (SEQ ID NO:47). The amino acid sequence encoded by this gene is shown as SEQ ID NO:48. NF-ATc is one of the components of a transcription factor. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 24 of FIG. 1.

[0324] When the nucleotide sequence of A4RS-492 was determined, this was identical with the sequence of GLI Kruppel-related protein [Accession: M77698] (SEQ ID NO:49). The amino acid sequence encoded by this gene is shown as SEQ ID NO:50. GLI Kruppel-related protein, which is also called YY1, is a suppressively functioning transcription factor. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 25 of FIG. 1.

[0325] When the nucleotide sequence of A4RS-507 was determined, this was identical with the sequence of human mRNA homologous to the p64 bovine chloride channel [Accession: Y12696] (SEQ ID NO:51). The amino acid sequence encoded by this gene is shown as SEQ ID NO:52. Only the sequence of this gene is reported, and its function is not clearly known. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 26 of FIG. 1.

[0326] When the nucleotide sequence of A4RS-514 was determined, this was identical with the sequence of KIAA0080 [Accession: D38522] (SEQ ID NO:53). The amino acid sequence encoded by this gene is shown as SEQ ID NO:54. The protein encoded by this gene is judged to be the human ortholog of rat synaptotagmin XI that is a membrane protein. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 27 of FIG. 1.

[0327] When the nucleotide sequence of A4RS-523 was determined, this was identical with the sequence of nicotinamide N-methyltransferase [Accession: U08021] (SEQ ID NO:55). The amino acid sequence encoded by this gene is shown as SEQ ID NO:56. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 28 of FIG. 1.

[0328] When the nucleotide sequence of A4RS-544 was determined, this was identical with the sequence of H. sapiens mRNA for surface glycoprotein [Accession: Z50022] (SEQ ID NO:57). The amino acid sequence encoded by this gene is shown as SEQ ID NO:58. The protein encoded by this gene is a type I membrane protein. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 29 of FIG. 1.

[0329] When the nucleotide sequence of A4RS-547 was determined, this was identical with the sequence of early growth response gene alpha (EGR-alpha) [Accession: S81439] (SEQ ID NO:59). The amino acid sequence encoded by this gene is shown as SEQ ID NO:60. EGR-alpha is a transcription factor, and it has been reported that its homologue, EGR-1, is activated by a shear stress in endothelial cells [Arterioscler. Thromb. Vasc. Biol., 17, 2280(1997)]. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 30 of FIG. 1.

[0330] When the nucleotide sequence of A4RS-557 was determined, this was identical with the sequence of SF2p33 [Accession: M69040] (SEQ ID NO:61). The amino acid sequence encoded by this gene is shown as SEQ ID NO:62. SF2p33 is a nuclear factor and is indispensable for the splicing of pre-mRNA. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 31 of FIG. 1.

[0331] When the nucleotide sequence of A4RS-577 was determined, this was identical with the sequence of p66 shc [Accession: U73377] (SEQ ID NO:63). The amino acid sequence encoded by this gene is shown as SEQ ID NO:64. shc is a signal transduction molecule which transduces a stimulus from tyrosine kinase to ras. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 32 of FIG. 1.

[0332] When the nucleotide sequence of A4RS-588 was determined, this was identical with the sequence of lysosomal acid lipase (LAL) [Accession: M74775] (SEQ ID NO:65). The amino acid sequence encoded by this gene is shown as SEQ ID NO:66. LAL, which is also called cholesteryl esterase, is an enzyme hydrolyzing cholesteryl esters incorporated into cells. If this gene is deficient, cholesteryl ester storage disease may be induced to cause arteriosclerosis. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 33 of FIG. 1.

[0333] When the nucleotide sequence of A4RS-602 was determined, this was identical with the sequence of N^G,N^G-dimethylarginine dimethylaminohydrolase (DDAH) [Accession: AB001915] (SEQ ID NO:67). The amino acid sequence

encoded by this gene is shown as SEQ ID NO:68. DDAH hydrolyzes N^G-monomethyl-L-arginine (MMA) and N^G,N^G-dimethyl-L-arginine (DMA) to citrullin. Since MMA and DMA are substrate analogs for NO synthase, they inhibit the synthesis of NO. That is, DDAH induces NO synthesis indirectly. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 34 of FIG. 1 and lane 11 of FIG. 3.

5 [0334] When the nucleotide sequence of A4RS-608 was determined, this was identical with the sequence of serum deprivation response (SDPR) [Accession: AF085481] (SEQ ID NO:69). The amino acid sequence encoded by this gene is shown as SEQ ID NO:70. For human SDPR, only its sequence is registered. It has been reported that the expression of its mouse ortholog, sdr, is induced by serum deprivation in NIH3T3. However, its function is unknown. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 35 of FIG. 1.

10 [0335] When the nucleotide sequence of A4RS-612 was determined, this was identical with the sequence of regulator of G protein signaling (RGS3) [Accession: U27655] (SEQ ID NO:71). The amino acid sequence encoded by this gene is shown as SEQ ID NO:72. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in panel 36 of FIG. 1.

15 [0336] When the nucleotide sequence of A4RS-625 was determined, this was identical with the sequence of cytokine-inducible nuclear protein C-193 [Accession: X83703] (SEQ ID NO:73). The amino acid sequence encoded by this gene is shown as SEQ ID NO:74. In endothelial cells, this gene is expressed in response to inflammatory stimuli such as TNF- α and LPS. The amino acid sequence encoded by this gene does not show substantial homology with other known proteins, but has been proved to be a nuclear factor. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 37 of FIG. 1.

20 [0337] When the nucleotide sequence of A4RS-666 was determined, this was identical with the sequence of laminin B1 chain [Accession: M61916] (SEQ ID NO:75). The amino acid sequence encoded by this gene is shown as SEQ ID NO:76. Laminin B1 chain is a glycoprotein and is a kind of extracellular matrix. It has been reported that, in bovine arterial endothelial cells, laminin protein is increased by the application of a shear stress [Laboratory Investigation, 73, 565(1995)]. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 38 of FIG. 1.

25 [0338] When the nucleotide sequence of A4RS-668 was determined, this was identical with the sequence of Matrix Gla protein (MGP) [Accession: M58549] (SEQ ID NO:77). The amino acid sequence encoded by this gene is shown as SEQ ID NO:78. MGP is a kind of extracellular matrix. It has been reported that, in knockout mice of this gene, calcification occurs in arteries and cartilages and results in death [Nature, 386, 78(1997)]. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 39 of FIG. 1.

30 [0339] When the nucleotide sequence of A4RS-674 was determined, this was identical with the sequence of PTX3 (SEQ ID NO:79). The amino acid sequence encoded by this gene is shown as SEQ ID NO:80. PTX3 is a member of the pentraxin family, and is a secreted factor having a signal sequence at the amino-terminus. It has been reported that, in vascular endothelial cells and monocytes, this gene is expressed in response to inflammatory stimuli such as IL-1 and TNF- α . Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 40 of FIG. 1.

35 [0340] When the nucleotide sequence of A4RS-682 was determined, this was identical with the sequence of connective tissue growth factor [Accession: X78947] (SEQ ID NO:81). The amino acid sequence encoded by this gene is shown as SEQ ID NO:82. Connective tissue growth factor is a secreted factor having a signal sequence at the amino-terminus, and its expression in developed arteriosclerotic lesions has been reported [Circulation, 95, 831(1997)]. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 41 of FIG. 1.

40 [0341] When the nucleotide sequence of A4RS-751 was determined, this was identical with the sequence of FLI-1 [Accession: Q50644] (SEQ ID NO:83). The amino acid sequence encoded by this gene is shown as SEQ ID NO:84. FLI-1, which is also called ERGB, is a transcription factor belonging to the ETS family. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 42 of FIG. 2.

45 [0342] When the nucleotide sequence of A4RS-781 was determined, this was identical with the sequence of HLA-E [Accession: X56841] (SEQ ID NO:85). The amino acid sequence encoded by this gene is shown as SEQ ID NO:86. HLA-E is a kind of MHC class I protein. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 43 of FIG. 2.

50 [0343] When the nucleotide sequence of A4RS-784 was determined, this was identical with the sequence of plasminogen activator inhibitor (PAI) [Accession: M16006] (SEQ ID NO:87). The amino acid sequence encoded by this gene is shown as SEQ ID NO:88. PAI acts antagonistically against plasminogen activator. It has been reported that its expression is decreased by the application of a shear stress [Blood, 87, 2314(1996)]. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 44 of FIG. 2 and lane 12 of FIG. 3.

55 [0344] When the nucleotide sequence of A4RS-817 was determined, this was identical with the sequence of keratin 18 [Accession: M26326] (SEQ ID NO:89). The amino acid sequence encoded by this gene is shown as SEQ ID NO: 90. Keratin 18 is a kind of intermediate filament. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 45 of FIG. 2.

[0345] When the nucleotide sequence of A4RS-818 was determined, this was identical with the sequence of human

secreted protein gene 5 clone HELDY41 [Accession: V34315] (SEQ ID NO:91). The amino acid sequence encoded by this gene is shown as SEQ ID NO:92. The amino acid sequence encoded by this gene coincides with a partial sequence of human hedgehog interacting protein [Accession: W56538]. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 46 of FIG. 2.

5 [0346] When the nucleotide sequence of A4RS-914 was determined, this was identical with the sequence of monocyte-derived neutrophil-activating protein (MONAP) [Accession: M26383] (SEQ ID NO:93). The amino acid sequence encoded by this gene is shown as SEQ ID NO:94. MONAP is also called interleukin 8 (IL-8), and its relation with the development of arteriosclerosis is strongly suggested. In fact, its strong expression in an mRNA level and in a protein level has been reported in macrophages derived from arteriosclerotic plaques [Arterioscler. Thromb. Vasc. Biol., 16, 1007(1996)]. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 47 of FIG. 2.

10 [0347] When the nucleotide sequence of A4RS-929 was determined, this was identical with the sequence of MUC18 glycoprotein [Accession: M28882] (SEQ ID NO:95). The amino acid sequence encoded by this gene is shown as SEQ ID NO:96. MUC18, which is also called Mel-CAM or CD146, is a cell adhesion factor having an immunoglobulin-like domain. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 48 of FIG. 2.

15 [0348] When the nucleotide sequence of A4RS-935 was determined, this was identical with the sequence of nuclear speckle-type protein (SPOP) [Accession: AJ000644] (SEQ ID NO:97). The amino acid sequence encoded by this gene is shown as SEQ ID NO:98. SPOP is a nuclear factor which is considered to interact with splicing factors. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 49 of FIG. 2.

20 [0349] When the nucleotide sequence of A4RS-938 was determined, this was identical with the sequence of thrombospondin (TSP) [Accession: X14787] (SEQ ID NO:99). The amino acid sequence encoded by this gene is shown as SEQ ID NO:100. TSP is a glycoprotein functioning as an extracellular matrix, and has an inhibitory effect on carcinogenesis and angiogenesis. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 50 of FIG. 2.

25 [0350] When the nucleotide sequence of A4RS-939 was determined, this was identical with the sequence of caveolin [Accession: Z18951] (SEQ ID NO:101). The amino acid sequence encoded by this gene is shown as SEQ ID NO:102. Caveolin is a principal component of caveolae present in the cell membrane. It has been reported that caveolin participates in the control of NO production by interacting with nitric oxide (NO) synthase [J. Biol. Chem., 273, 34724 (1998)]. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 51 of FIG. 2.

30 [0351] When the nucleotide sequence of A4RS-945 was determined, this was identical with the sequence of human BENE mRNA [Accession: U17077] (SEQ ID NO:103). The amino acid sequence encoded by this gene is shown as SEQ ID NO:104. BENE is a membrane protein having homology with T cell surface glycoprotein MAL. Since its expression in endothelial cells is increased by lysophosphatidyl choline (lysoPC) that is a component of oxidized lipoproteins, its relation with arteriosclerosis is suggested [J. Biochemistry, 123, 1119(1998)]. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 52 of FIG. 2.

35 [0352] When the nucleotide sequence of A4RS-947 was determined, this was identical with the sequence of 1,4-alpha-glucan branching enzyme [Accession: L07956] (SEQ ID NO:105). The amino acid sequence encoded by this gene is shown as SEQ ID NO:106. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 53 of FIG. 2.

40 [0353] When the nucleotide sequence of A4RS-948 was determined, this was identical with the sequence of ferritin H [Accession: M11146] (SEQ ID NO:107). The amino acid sequence encoded by this gene is shown as SEQ ID NO:108. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 54 of FIG. 2.

45 [0354] When the nucleotide sequence of A4RS-949 was determined, this was identical with the sequence of human PAST (HPAST) [Accession: AF001434] (SEQ ID NO:109). The amino acid sequence encoded by this gene is shown as SEQ ID NO:110. HPAST has homology with PAST-1 that is a fly-derived glycoprotein. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 55 of FIG. 2.

(3) Novel partial-length genes exhibiting a shear stress-dependent increase of expression

50 [0355] When the nucleotide sequence of A4RS-011 was determined, this was identical with a group of ESTs included in UniGene Hs. 71475. The sequence represented by SEQ ID NO: 111 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:112. The amino acid sequence encoded by this sequence does not show substantial homology with other known proteins. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 56 of FIG. 2.

55 [0356] When the nucleotide sequence of A4RS-115 was determined, this was identical with a group of ESTs included in UniGene Hs. 3742. The sequence represented by SEQ ID NO:113 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:114. This gene has very high homology with rat SEC61 [Accession: M96630] and is considered to be the human ortholog thereof. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 57 of FIG. 2 and lane 13 of FIG. 3.

[0357] When the nucleotide sequence of A4RS-143 was determined, this was identical with a group of ESTs included in UniGene Hs. 5307. The sequence represented by SEQ ID NO:115 could be obtained by joining the corresponding ESTs together. This sequence does not have an ORF consisting of 50 or more amino acids and is hence considered to be a non-translational region. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 58 of FIG. 2 and lane 14 of FIG. 3.

[0358] When the nucleotide sequence of A4RS-171 was determined, no sequence identical exactly with it was found in the data banks. The nucleotide sequence is shown as SEQ ID NO: 116. This sequence does not have an ORF consisting of 50 or more amino acids and is hence considered to be a non-translational region. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 59 of FIG. 2.

[0359] When the nucleotide sequence of A4RS-193 was determined, this was identical with a group of ESTs included in UniGene Hs. 112157. The sequence represented by SEQ ID NO:117 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO: 118. The protein encoded by this sequence does not show substantial homology with other known proteins. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 60 of FIG. 2 and lane 15 of FIG. 3.

[0360] When the nucleotide sequence of A4RS-280 was determined, this was identical with a group of ESTs included in UniGene Hs. 109017. The sequence represented by SEQ ID NO:119 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:120. This gene has as high as 87% homology with human ras-like protein TC10 [Accession: M31470] and is considered to be a novel human low-molecular-weight GTP-binding protein. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 61 of FIG. 2 and lane 16 of FIG. 3.

[0361] When the nucleotide sequence of A4RS-402 was determined, this was identical with a group of ESTs included in UniGene Hs. 181077. The sequence represented by SEQ ID NO:121 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:122. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 62 of FIG. 2 and lane 17 of FIG. 3.

[0362] When the nucleotide sequence of A4RS-533 was determined, this was identical with EST clones R07925 and T86046. The sequence represented by SEQ ID NO:123 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:124. The amino acid sequence encoded by this sequence does not show substantial homology with other known proteins. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 63 of FIG. 2.

[0363] When the nucleotide sequence of A4RS-604 was determined, this was identical with a group of ESTs included in UniGene Hs. 34160. The sequence represented by SEQ ID NO:125 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:126. The protein encoded by this sequence does not show substantial homology with other known proteins. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 64 of FIG. 2 and lane 18 of FIG. 4.

[0364] When the nucleotide sequence of A4RS-615 was determined, this was identical with a group of ESTs included in UniGene Hs. 193974. The sequence represented by SEQ ID NO:127 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:128. The protein encoded by this sequence does not show significant homology with other known proteins. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 65 of FIG. 2.

[0365] When the nucleotide sequence of A4RS-619 was determined, this was identical with a group of ESTs included in UniGene Hs. 14512. The sequence represented by SEQ ID NO:129 could be obtained by joining the corresponding ESTs together. This sequence does not have an ORF consisting of 50 or more amino acids and is hence considered to be a non-translational region. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 66 of FIG. 2.

[0366] When the nucleotide sequence of A4RS-626 was determined, no sequence identical exactly with it was found in the data banks. The nucleotide sequence is shown as SEQ ID NO:130. This sequence does not have an ORF consisting of 50 or more amino acids and is hence considered to be a non-translational region. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 67 of FIG. 2 and lane 19 of FIG. 4.

[0367] When the nucleotide sequence of A4RS-676 was determined, this was identical with a group of ESTs included in UniGene Hs. 8881. The sequence represented by SEQ ID NO:131 could be obtained by joining the corresponding ESTs together. This sequence does not have an ORF consisting of 50 or more amino acids and is hence considered to be a non-translational region. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 68 of FIG. 2.

[0368] When the nucleotide sequence of A4RS-679 was determined, no sequence identical exactly with it was found in the data banks. The nucleotide sequence is shown as SEQ ID NO: 132. This sequence does not have an ORF consisting of 50 or more amino acids and is hence considered to be a non-translational region. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 69 of FIG. 2.

[0369] When the nucleotide sequence of A4RS-737 was determined, no sequence identical exactly with it was found

in the data banks. The nucleotide sequence is shown as SEQ ID NO:133. This sequence does not have an ORF consisting of 50 or more amino acids and is hence considered to be a non-translational region. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 70 of FIG. 2.

[0370] When the nucleotide sequence of A4RS-780 was determined, this was identical with a group of ESTs included in UniGene Hs. 34489. The sequence represented by SEQ ID NO:134 could be obtained by joining the corresponding ESTs together. This sequence does not have an ORF consisting of 50 or more amino acids and is hence considered to be a non-translational region. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 71 of FIG. 2.

[0371] When the nucleotide sequence of A4RS-826 was determined, this was identical with a group of ESTs included in UniGene Hs. 7348. The sequence represented by SEQ ID NO:135 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:136. The protein encoded by this sequence does not show substantial homology with other known proteins. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 72 of FIG. 2.

[0372] When the nucleotide sequence of A4RS-916 was determined, this was identical with a group of ESTs included in UniGene Hs. 105695. The sequence represented by SEQ ID NO:137 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:138. The protein encoded by this sequence does not show substantial homology with other known proteins. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 73 of FIG. 2 and lane 20 of FIG. 4.

[0373] When the nucleotide sequence of A4RS-933 was determined, this was identical with EST clone A1391599. The sequence represented by SEQ ID NO:139 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:140. The protein encoded by this sequence does not show substantial homology with other known proteins. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 74 of FIG. 2.

[0374] When the nucleotide sequence of A4RS-943 was determined, this was identical with a group of ESTs included in UniGene Hs. 186838. The sequence represented by SEQ ID NO:141 could be obtained by joining the corresponding ESTs together. The amino acid sequence encoded by this sequence is shown as SEQ ID NO:142. The amino acid sequence encoded by this sequence has a zinc finger motif and shows 67% homology with bird-derived zinc finger 5 protein [Accession: U51640]. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in lane 75 of FIG. 2.

Example 5

Cloning of full-length cDNAs

[0375] With respect to the novel DNAs exhibiting a shear stress-dependent increase of expression which were obtained in Example 3, the length of the insert was significantly shorter than the size of mRNA detected by Northern blotting in most cases. That is, the clones obtained from the subtraction library were judged to be partial cDNA fragments and not full-length cDNAs. Accordingly, with respect to eight of the novel DNAs, their full-length cDNAs were obtained again from a cDNA library.

(1) Construction of a cDNA library using a λ phage vector

[0376] Three point two μ g of oligo(dT)-XhoI primer (SEQ ID NO:160) was added to 4.8 μ g of the HUVEC-derived poly(A)⁺ RNA obtained in Example 1. Then, distilled water was added thereto so as to make a volume of 6.8 μ l. This solution was heated at 70°C for 10 minutes and then cooled rapidly by placing it on ice. To this solution, 4 μ l of 5 x reverse transcriptase reaction buffer (attached to the enzyme), 2 μ l of 100 mM DTT, 1.2 μ l of a mixed dNTP solution [10 mM dATP, 10 mM dGTP, 10 mM dTTP, 5 mM 5-methyl dCTP], and 1 μ l of [α -³²P]dATP (110 TBq/mmol; manufactured by Amersham Pharmacia Biotech) as a tracer were added on ice. After this mixture was kept at 37°C for 2 minutes, 5 μ l of Superscript II RNase H⁻ Reverse Transcriptase (1,000 units; manufactured by Life Technologies) was added thereto and reacted at 44°C for 1 hour to synthesize cDNA. After the reaction was stopped by the addition of 0.8 μ l of 0.5 M EDTA (pH 8.0), the reaction mixture was subjected to a phenol-chloroform treatment and a chloroform treatment, and precipitated with ethanol to recover a cDNA-mRNA hybrid. After the precipitate was dissolved in 17 μ l of distilled water, 5 μ l of 5 x reaction buffer (attached to the enzyme), 2.5 μ l of 100 μ M dGTP, and 0.5 μ l of 15 units/ μ l terminal deoxynucleotidyl transferase (manufactured by Life Technologies) were added thereto. This mixture was reacted at 37°C for 30 minutes to add oligo-dG to the 3'-terminus of cDNA. After the reaction was stopped by the addition of 5 μ l of 0.5 M EDTA (pH 8.0), the reaction mixture was subjected to a phenol-chloroform treatment and a chloroform treatment, and precipitated with ethanol. After the resulting precipitate was dissolved in 20.7 μ l of distilled water, 1.5 μ l of reaction buffer A [200 mM Tris-HCl (pH 8.75), 100 mM KCl, 100 mM (NH₄)₂SO₄, 20 mM MgSO₄, 1% Triton X-100, 1

mg/ml BSA], 1.5 µl of reaction buffer B [200 mM Tris-HCl (pH 9.2), 600 mM KCl, 20 mM MgCl₂], 0.3 µg of oligo(dC) NotI primer (SEQ ID NO:161), 0.75 µl of a 10 mM mixed dNTP solution, and 1.5 µl of 10 mM β-NAD were added thereto so as to make a total volume of 27.45 µl. After this mixture was kept at 55°C for 5 minutes, 1.5 µl of 5 units/µl ExTaq DNA polymerase (manufactured by Takara Shuzo Co., Ltd.), 0.75 µl of 100 units/µl Ampligase (manufactured by Epicentre), and 0.3 µl of 5 units/µl Hybridase (manufactured by Epicentre) were added thereto. Using a Thermal Cycler DNA Engine (manufactured by MJ Research), the temperature of this mixture was slowly reduced from 55°C to 35°C at a rate of 0.3°C per minute. Thereafter, the mixture was kept at 35°C for 15 minutes to anneal the primer to the template single-stranded cDNA. Thereafter, the mixture was kept at 72°C for 15 minutes to carry out the extension reaction of second-strand DNA. By repeating this annealing/extension cycle three more times, mRNA was degraded to make double-stranded cDNA. To the reaction mixture, 0.5 µl of 0.5 M EDTA (pH 8.0), 0.5 µl of 10% SDS, and 0.5 µl of 20 µg/µl Proteinase K were added. Then, the reaction mixture was kept at 45°C for 15 minutes to stop the reaction and inactivate the enzyme. Thereafter, the reaction mixture was subjected to a phenol-chloroform treatment and a chloroform treatment, and precipitated with ethanol. The resulting precipitate was dissolved in 44 µl of distilled water. Then, 5 µl of 10 x reaction buffer (attached to the enzyme) and 1 µl of XhoI (10 units/µl; manufactured by Takara Shuzo Co., Ltd.) were added thereto and reacted at 37°C for 2 hours to cleave the XhoI site in the oligo(dT)-XhoI primer. Then, 0.5 µl of 5 M NaCl and 1 µl of NotI (10 units/µl; manufactured by Takara Shuzo Co., Ltd.) were added to the reaction mixture and reacted at 37°C for 2 hours to cleave the NotI site in the oligo(dC)-NotI primer. In order to remove short cDNA fragments of not greater than 400 bp size, and unreacted primers and nucleotides, the reaction mixture was placed on a SizeSep-400 spun column (manufactured by Amersham Pharmacia Biotech) equilibrated with TE buffer, and centrifuged at 400 x g for 2 minutes. The resulting eluate was purified by subjecting it to a phenol-chloroform treatment and a chloroform treatment. Eight µl of 10 x reaction buffer (manufactured by Takara Shuzo Co., Ltd.), 62 µl of distilled water, and 50 units (5 µl) of XhoI were added to 5 µg (5 µl) of cloning vector λZAPII (manufactured by Stratagene), and reacted at 37°C for 4 hours. Then, 1 µl of 5 M NaCl and 50 units (5 µl) of NotI were added to the reaction mixture, and further reacted at 37°C for 4 hours. Thus, the XhoI and NotI sites of the vector were cleaved. Then, 9 µl of 10 x reaction buffer (attached to the enzyme) and 0.025 unit of temperature-sensitive alkaline phosphatase (manufactured by Life Technologies) were added to the reaction mixture and reacted at 65°C for 15 minutes to dephosphorylate the 5'-termini of the XhoI-cleaved end and NotI-cleaved end of the vector. After the reaction was stopped by the addition of 10 µl of a reaction stopper (attached to the enzyme), the reaction mixture was subjected to a phenol-chloroform treatment and a chloroform treatment, and the vector was recovered by ethanol precipitation. The aforesaid purified cDNA was added to 0.25 µg of the vector, followed by ethanol precipitation. The recovered vector DNA and cDNA were dissolved in 4 µl of a ligase buffer [100 mM Tris-HCl (pH 7.6), 5 mM MgCl₂, 300 mM NaCl], and 4 µl of solution B in a Ligation Kit Ver. 1 (manufactured by Takara Shuzo Co., Ltd.). This mixture was reacted at 26°C for 10 minutes to ligate cDNA to vector DNA. Using 4 µl portions of the reaction mixture, packaging was carried out using a λ Phage Packaging Extract Gigapack β Gold (manufactured by Stratagene). Specifically, reagents were used and the procedure for packaging was carried out according to the manual attached to the kit. *Escherichia coli* XL1-Blue MRF' strain was infected with the resulting phage, and its titer was measured. Moreover, the phage was multiplied on a plate and recovered in SM buffer (its composition is described in the manual of Stratagene). Thus, the cDNA library was amplified once to obtain a final cDNA library. Specifically, the procedures for titer measurement and library amplification were carried out according to the manual attached to the λ phage packaging kit.

(2) Obtaining of full-length cDNAs by plaque hybridization

[0377] With respect to the library constructed in step (1), plaque DNAs were blotted to a nylon membrane Hybond N+ (manufactured by Amersham Pharmacia Biotech). The plasmids derived from the subtraction library obtained in Example 2 were used as templates, and primers specific for each gene were synthesized and used. After a PCR DIG labeling mix (manufactured by Boehringer Mannheim) was added, PCR was carried out to amplify and label each gene-specific fragments. Using these DNA fragments as probes, hybridization and the detection of positive plaques were carried out according to the manual of Boehringer Mannheim. Positive plaques were amplified in SM buffer and formed into plasmids using helper phage ExAssist (manufactured by Stratagene). Specifically, the procedure for plasmid formation was carried out according to the manual of Stratagene.

(2) Determination of nucleotide sequence

[0378] The nucleotide sequence of each of the cDNA clones thus obtained was determined by means of a 377 DNA Sequencer (manufactured by Perkin Elmer). Specifically, the determination of the nucleotide sequence was carried out with a Dye Primer Cycle Sequencing FS Ready Reaction Kit according to the manual attached to the Kit (manufactured by Perkin Elmer). Moreover, this nucleotide sequence was translated into an amino acid sequence on a three-frame basis and examined for the presence of an open reading frame (ORF).

(3) Homology analysis of full-length cDNAs

① A4RS-002

[0379] With respect to the full-length cDNA clone pA4RS-002-1 obtained as a result of plaque hybridization, the whole nucleotide sequence of cDNA was determined and the resulting nucleotide sequence is shown as SEQ ID NO: 143. *Escherichia coli* DH5 α strain having clone pA4RS-002-1 introduced thereinto (*Escherichia coli* DH5 α /pA4RS-002-1) was internationally deposited on August 5, 1999 with the National Institute of Bioscience and Human-Technology, the Agency of Industrial Science and Technology (Higashi 1-1-3, Tsukuba City, Ibaraki Prefecture, Japan) under the Budapest Treaty, and assigned the accession number FERM BP-6822. In the nucleotide sequence of A4RS-002, an ORF consisting of 390 amino acids was observed (its amino acid sequence is shown as SEQ ID NO:144). As a result of homology analysis, this amino acid sequence was found to show significant homology with proteins belonging to the immunoglobulin family. Among others, this amino acid sequence show high homology with A33 antigen that is a specific marker for human colon carcinoma [Proc. Natl. Acad. Sci. USA, 94, 469(1997)] and CAR (coxackie and adenovirus receptor) that is a virus receptor protein [Science, 275, 1320(1997)]. Judging from their primary structure, these factors are presumed to be a type I membrane protein. According to a hydrophilicity analysis on the basis of the amino acid sequence, 29 residues at the amino-terminus of A4RS-002 is estimated to be a secretion signal, and a sequence extending from the 249th to 270th amino acid is considered to be a highly hydrophobic transmembrane region. Since ICAM-1 and VCAM-1 belonging to the immunoglobulin family exhibit a shear stress-dependent alteration of expression, A4RS-002 is presumed to belong to the immunoglobulin family and function as a membrane protein. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 76 of FIG. 2 and lane 21 of FIG. 4.

② A4RS-049

[0380] With respect to the full-length cDNA clone pA4RS-049-1 obtained as a result of plaque hybridization, the whole nucleotide sequence of cDNA was determined and the resulting nucleotide sequence is shown as SEQ ID NO: 145. *Escherichia coli* DH5 α strain having clone pA4RS-049-1 introduced thereinto (*Escherichia coli* DH5 α /pA4RS-049-1) was internationally deposited on August 5, 1999 with the National Institute of Bioscience and Human-Technology, the Agency of Industrial Science and Technology (Higashi 1-1-3, Tsukuba City, Ibaraki Prefecture, Japan) under the Budapest Treaty, and assigned the accession number FERM BP-6823. In the nucleotide sequence of A4RS-049, an ORF consisting of 881 amino acids was observed (its amino acid sequence is shown as SEQ ID NO:146). As a result of homology analysis, the protein encoded by A4RS-049 showed significant homology not only with mouse-derived 3BP-1 (SH3 domain binding protein) [EMBO, J. 14, 3127(1995)], but also with various GTPase-activating protein (GAPs) such as rhoGAP and Abr. GAPs are a family of proteins controlling the GTPase activity of low-molecular-weight GTP-binding proteins such as ras and rab, and A4RS-049 shows homology with GAPs (e.g., rho and rac) specific for a subfamily considered to participate in regulation of cytoskeleton. In the amino acid sequence encoded by A4RS-049, the GTPase-activating domain conserved among known GAPs is present. Accordingly, A4RS-049 is presumed to function as a GAP. Moreover, a nematode-derived gene [Accession: Z73425] and a yeast-derived gene [Accession: Z97210], which are registered in databases but have an unknown function, show significant homology with the protein encoded by A4RS-049. Thus, A4RS-049 is expected to be a gene conserved well in the process of evolution. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 77 of FIG. 2 and lane 22 of FIG. 4.

③ A4RS-230

[0381] With respect to the full-length cDNA clone pA4RS-230-2 obtained as a result of plaque hybridization, the whole nucleotide sequence of cDNA was determined and the resulting nucleotide sequence is shown as SEQ ID NO: 147. *Escherichia coli* DH5 α strain having clone pA4RS-230-2 introduced thereinto (*Escherichia coli* DH5 α /pA4RS-230-2) was internationally deposited on August 5, 1999 with the National Institute of Bioscience and Human-Technology, the Agency of Industrial Science and Technology (Higashi 1-1-3, Tsukuba City, Ibaraki Prefecture, Japan) under the Budapest Treaty, and assigned the accession number FERM BP-6824.

[0382] In the nucleotide sequence of A4RS-230, an ORF consisting of 322 amino acids was observed (its amino acid sequence is shown as SEQ ID NO:148). As a result of homology analysis, the protein encoded by A4RS-230 shows as high as 83% homology with mouse myeloid upregulated protein [Accession: 035682] and is considered to be a human counterpart thereof. However, its part on the C-terminal side is substantially different. As to mouse myeloid upregulated protein, only the sequence is registered in a database and its function is unknown. According to a hydrophilicity analysis on the basis of the amino acid sequence, the protein encoded by A4RS-230 has very high hydro-

phobicity and may hence function as a membrane protein. However, a sequence judged to be a signal sequence is not present at the N-terminus. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 78 of FIG. 2 and lane 23 of FIG. 4.

④ A4RS-239

[0383] With respect to the full-length cDNA clone pA4RS-239-2 obtained as a result of plaque hybridization, the whole nucleotide sequence of cDNA was determined and the resulting nucleotide sequence is shown as SEQ ID NO: 149. *Escherichia coli* DH5 α strain having clone pA4RS-239-2 introduced thereinto (*Escherichia coli* DH5 α /pA4RS-239-2) was internationally deposited on August 5, 1999 with the National Institute of Bioscience and Human-Technology, the Agency of Industrial Science and Technology (Higashi 1-1-3, Tsukuba City, Ibaraki Prefecture, Japan) under the Budapest Treaty, and assigned the accession number FERM BP-6825.

[0384] In the nucleotide sequence of A4RS-239, an ORF consisting of 663 amino acids was observed (its amino acid sequence is shown as SEQ ID NO:150). As a result of homology analysis, the protein encoded by A4RS-239 showed low but significant homology with various GAPs such as rhoGAP and Abr, similarly to the above-described A4RS-049. However, A4RS-239 and A4RS-049 are different DNAs. In the amino acid sequence encoded by A4RS-239, the GTPase-activating domain conserved among known GAPs is present. Accordingly, A4RS-239 is presumed to function as a GAP. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 79 of FIG. 2 and lane 24 of FIG. 3.

⑤ A4RS-242

[0385] With respect to the full-length cDNA clone pA4RS-242-1 obtained as a result of plaque hybridization, the whole nucleotide sequence of cDNA was determined and the resulting nucleotide sequence is shown as SEQ ID NO: 151. *Escherichia coli* DH5 α strain having clone pA4RS-242-1 introduced thereinto (*Escherichia coli* DH5 α /pA4RS-242-1) was internationally deposited on August 5, 1999 with the National Institute of Bioscience and Human-Technology, the Agency of Industrial Science and Technology (Higashi 1-1-3, Tsukuba City, Ibaraki Prefecture, Japan) under the Budapest Treaty, and assigned the accession number FERM BP-6826. In the nucleotide sequence of A4RS-242, an ORF consisting of 863 amino acids was observed (its amino acid sequence is shown as SEQ ID NO:152). As a result of homology analysis, the amino-terminal half of the protein encoded by A4RS-242 is identical with approximately the full length of the product of the gene ehb10. However, a part of A4RS-242 corresponding to the half on the carboxyl-terminal side is not present in ehb10. That is, they are considered to be splicing variants. ehb10 is one of the proteins obtained by expression cloning, as factors binding to the EH domain considered to participate in the protein interaction of Eps15 (the substrate for EGF receptor) [Genes & Dev., 11, 2239(1997)], but its function is unknown. However, the motif required for binding to the EH domain is also present in A4RS-242. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 80 of FIG. 2 and lane 25 of FIG. 4.

⑥ A4RS-491

[0386] With respect to the full-length cDNA clone pA4RS-491-1 obtained as a result of plaque hybridization, the whole nucleotide sequence of cDNA was determined and the resulting nucleotide sequence is shown as SEQ ID NO: 153. *Escherichia coli* DH5 α strain having clone pA4RS-491-1 introduced thereinto (*Escherichia coli* DH5 α /pA4RS-491-1) was internationally deposited on August 5, 1999 with the National Institute of Bioscience and Human-Technology, the Agency of Industrial Science and Technology (Higashi 1-1-3, Tsukuba City, Ibaraki Prefecture, Japan) under the Budapest Treaty, and assigned the accession number FERM BP-6827. In the nucleotide sequence of A4RS-491, an ORF consisting of 331 amino acids was observed (its amino acid sequence is shown as SEQ ID NO:154). As a result of homology analysis, the protein encoded by A4RS-491 was identical with an amino acid sequence [Accession: 043334] registered in a database as a human hypothetical protein over a wide range. However, this hypothetical protein consists of 393 amino acids, and it has been found that its 88th to 148th amino acids are not contained in the amino acid sequence encoded by A4RS-491. That is, they are considered to be splicing variants. The protein encoded by A4RS-491 shows substantial homology with nematode-derived glycerophosphodiester phosphodiesterase [Accession: Z78198] and bacterium-derived glycerophosphodiester phosphodiesterase [Accession: E69827], and has been found to be a gene conserved well in the process of evolution. It is known that bacterium-derived glycerophosphodiester phosphodiesterase is present on membranes. According to a hydrophilicity analysis on the basis of the amino acid sequence encoded by A4RS-491, an amino acid sequence extending from the 1st to 26th amino acid in SEQ ID NO: 154 is presumed to be a signal peptide. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 81 of FIG. 2 and lane 26 of FIG. 4.

⑦ A4RS-578

[0387] With respect to the full-length cDNA clone pA4RS-578-1 obtained as a result of plaque hybridization, the whole nucleotide sequence of cDNA was determined and the resulting nucleotide sequence is shown as SEQ ID NO: 155. *Escherichia coli* DH5 α strain having clone pA4RS-578-1 introduced thereto (*Escherichia coli* DH5 α /pA4RS-578-1) was internationally deposited on August 5, 1999 with the National Institute of Bioscience and Human-Technology, the Agency of Industrial Science and Technology (Higashi 1-1-3, Tsukuba City, Ibaraki Prefecture, Japan) under the Budapest Treaty, and assigned the accession number FERM BP-6828. In the nucleotide sequence of A4RS-578, an ORF consisting of 541 amino acids was observed (its amino acid sequence is shown as SEQ ID NO:156). As a result of homology analysis, the protein encoded by A4RS-578 showed the highest homology with the amino acid sequence [Accession: Z95559] of a protein of unknown function registered as a nematode-derived hypothetical protein, and then showed significant homology with rat brain finger protein (BFP) [Biochem. Biophys. Res. Commun., 240, 8 (1997)]. Rat BFP was cloned as a novel gene having the RING finger motif as a kind of zinc finger motif, and it has been reported that this gene is expressed brain-specifically and that the expression of this gene may be induced at the stage of differentiation into nerve cells. However, a sequence judged to be the RING finger motif is not present in the amino acid sequence encoded by A4RS-578. The protein encoded by A4RS-578 also shows significant homology with various GTP-binding proteins, and has two of the three motifs possessed in common by many GTP-binding proteins. Since the existence of GTP-binding proteins having only two motifs has been reported, there is a possibility that the protein encoded by A4RS-578 functions as a GTP-binding protein. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 82 of FIG. 2 and lane 27 of FIG. 4.

⑧ A4RS-829

[0388] With respect to the full-length cDNA clone pA4RS-829-1 obtained as a result of plaque hybridization, the whole nucleotide sequence of cDNA was determined and the resulting nucleotide sequence is shown as SEQ ID NO: 157. *Escherichia coli* DH5 α strain having clone pA4RS-829-1 introduced thereto (*Escherichia coli* DH5 α /pA4RS-829-1) was internationally deposited on August 5, 1999 with the National Institute of Bioscience and Human-Technology, the Agency of Industrial Science and Technology (Higashi 1-1-3, Tsukuba City, Ibaraki Prefecture, Japan) under the Budapest Treaty, and assigned the accession number FERM BP-6829. In the nucleotide sequence of A4RS-829, an ORF consisting of 173 amino acids was observed (its amino acid sequence is shown as SEQ ID NO:158). As a result of homology analysis, the protein encoded by A4RS-829 showed substantial homology with the amino acid sequences of proteins of unknown functions registered as hypothetical proteins, such as an arabidopsis-derived protein [Accession: Q48707], a nematode-derived protein [Accession: Q20340] and a yeast-derived protein [Accession: Q03677], and was found to be a gene conserved well in the process of evolution. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in lane 83 of FIG. 2 and lane 28 of FIG. 4.

Example 6Production of a recombinant protein of A4RS-002

(1) Construction of an expression plasmid

[0389] To 2 μ g of pA4RS-002-1 obtained in Example 5, 5 μ l of 10-reaction buffer (attached to the enzyme), 1 μ l of *Xho*I (10 units/ μ l; manufactured by Takara Shuzo Co., Ltd.), and distilled water were added so as to make a total volume of 50 μ l. This mixture incubated at 37°C for 2 hours to digest the cDNA completely. Then, 0.5 μ l of 5 M NaCl and 1 μ l of *Not*I (10 units/ μ l; manufactured by Takara Shuzo Co., Ltd.) were added to the reaction mixture. This mixture incubated at 37°C for 2 hours to digest the cDNA completely. The reaction mixture was subjected to a phenol-chloroform treatment and a chloroform treatment, and then precipitated with ethanol. After the resulting precipitate was dissolved in 20 μ l of distilled water, 3 μ l of 10 x blunting buffer (attached to the enzyme), 6 μ l of a 2.5 mM mixed dNTP solution, and 1 μ l of Klenow fragment (manufactured by Takara Shuzo Co., Ltd.) were added thereto. This mixture was incubated at 37°C for 1 hour to carry out the blunting of restriction enzyme-treated ends. The reaction mixture was subjected to a phenol-chloroform treatment and a chloroform treatment, and then precipitated with ethanol. After the resulting precipitate was dissolved in 5 μ l of distilled water, 0.4 μ g and 0.3 μ g, respectively, of *Sfi*I linkers (5'-CTTTAGAGCAC-3', 5'-CTCTAAAG-3') were added thereto so as to make a volume of 6 μ l. Twelve μ l of solution I and 6 μ l of solution II of a Ligation Kit Ver. 2 (manufactured by Takara Shuzo Co., Ltd.) were added thereto, and the resulting mixture was incubated at 16°C overnight to carry out linker ligation. The total amount of the reaction mixture was electrophoresed through 0.8% agarose gel, and the desired fragments were recovered using a QIAEX II Gel Extraction Kit (manufactured by QIAGEN). The procedure therefor was carried out according to the manual attached to the kit. The recovered DNA fragments

were dissolved in 10 μ l of distilled water. To this insert DNA, an animal cell expression plasmid vector pAMo [J. Biol. Chem., 268, 22782(1993); also called pAMoPRC3Sc (Japanese Published Unexamined Patent Application No. 336963/93)], which had been linearized with *Sfi*I and similarly recovered from an agarose gel, was added in a molar amount equal to 1/5 of that of the insert, and Ligation High (manufactured by Toyobo Co., Ltd.) in a volume equal to that of the solution. This mixture was incubated at 16°C for 3 hours to ligate the insert with linkers to the vector, and then introduced into competent-cell *Escherichia coli* MW294. After introduction, LB agar medium containing 50 μ g/ml ampicillin was inoculated with the bacterial suspension and incubated at 37°C overnight to form colonies. The resulting colonies were randomly picked up, and the plasmid was obtained from each colony and examined for the presence or absence of the insert by a restriction enzyme treatment. With respect to the colonies having the insert, the direction of the insert was examined. Using one clone, pAMo-002, having the desired directivity, the plasmid was mass-prepared using a QIAGEN Plasmid Midi Kit (manufactured by QIAGEN). The procedure therefor was carried out according to the manual attached to the kit. This plasmid was sterilely precipitated with ethanol and then dissolved in distilled water to a concentration of 1 μ g/ μ l. The above-described construction of pAMo-002 is illustrated in FIG. 5.

(2) Introduction of the recombinant plasmid into cultured animal cells

[0390] Namalwa KJM-1 [Cytotechnology, 1, 151(1988)], which is a host cell for gene expression, was collected by centrifugation, washed with 10 ml of K-PBS [13.7 mM KCl, 0.27 mM NaCl, 0.81 mM Na₂HPO₄, 0.15 mM KH₂PO₄, 0.4 mM MgCl₂], and suspended in cooled K-PBS so as to have a density of 8×10^6 cells/ml. Two hundred μ l (1.6×10^6 cells) of this cell suspension was mixed with 4 μ l (4 μ g) of the plasmid DNA prepared in step (1), and this mixture was quickly transferred to a chamber (manufactured by BIO-RAD) which had previously been cooled on ice. Then, using a Gene Pulser (manufactured by BIO-RAD), electroporation was carried out by the application of a voltage of 0.35 kV, 125 μ F. Thereafter, the chamber was quickly placed on ice, and the electroporated cells were transferred to a flask containing 8 ml of RPMI1640 medium (manufactured by Nissui Seiyaku Co., Ltd.). After the flask was incubated for 24 hours under conditions include 37°C and 5% CO₂, G-418 as an agent for selection was added thereto so as to give a final concentration of 0.5 mg/ml. Gene-introduced cells were selected by continuing the incubation for one more week. As a control, KJM-1 cells into which only pAMo vector having no insert was introduced were also prepared.

Example 7

Cloning of full-length cDNAs (2)

[0391] Similarly to Example 5, with respect to three novel partial cDNA fragments obtained from the subtraction library, full-length cDNAs were obtained from full-length cDNA libraries derived from human adipose tissue or Kato III.

(1) Construction of full-length cDNA libraries derived from human adipose tissue or Kato III cells

[0392] mRNA was extracted from human adipose tissue according to the method described in the paper (J. Sambrook, E.F. Fritsch & T. Maniatis, Molecular Cloning, Second Edition, Cold Spring Harbor Laboratory Press, 1989). Moreover, poly(A)⁺ RNA was purified with oligo-dT cellulose.

[0393] Similarly, mRNA was extracted from Kato III cells according to the method described in the paper (J. Sambrook, E.F. Fritsch & T. Maniatis, Molecular Cloning, Second Edition, Cold Spring Harbor Laboratory Press, 1989). Moreover, poly(A)⁺ RNA was purified with oligo-dT cellulose.

[0394] From each poly(A)⁺ RNA, a cDNA library was constructed according to an oligo-cap method [M. Maruyama and S. Sugano, Gene, 138, 171-174(1994)]. Using an oligo-cap linker (SEQ ID NO:162) and an oligo-dT primer (SEQ ID NO:163), BAP (Bacterial Alkaline Phosphatase) treatment, TAP (Tobacco Acid Phosphatase) treatment, RNA ligation, the synthesis of first-strand cDNA, and the removal of RNA were carried out according to the methods described in the paper [Suzuki & Kanno, Tanpakushitsu-Kakusan-Koso (in Japanese), 41:197-201(1996); Y. Suzuki, Gene, 200, 149-156(1997)]. Then, the resulting cDNA was converted to double-stranded cDNA by PCR using two primers [a 5'-terminal sense primer (SEQ ID NO:164) and a 3'-terminal antisense primer (SEQ ID NO:165)], and then cleaved with *Sfi*I. This PCR was carried out in such a way that, using a commercially available GeneAmp XL PCR Kit (manufactured by Perkin Elmer), the reaction mixture was heat-treated at 95°C for 5 minutes, subjected 12 times to a reaction cycle comprising heating at 95°C for 1 minute, 58°C for 1 minute, and at 72°C for 10 minutes, and then kept at 4°C. Thereafter, a cDNA library was constructed by cloning the cDNA into a *Dra*III-cleaved pME18SFL3 vector [Accession: AB009864; expression vector, 3392 bp] with the fixed directivity of the cDNA.

(2) Determination of the full-length cDNA sequences

[0395] With respect to the plasmid DNAs of clones obtained from the cDNA libraries prepared in step (1), each cDNA clone was subjected to an in vitro transposon (hereinafter abbreviated as Tn) transposition reaction by using a GSP-1 Genome Priming System (manufactured by NEB). pGPS1.1 (manufactured by NEB) was used as the Tn donor. After completion of the Tn transposition reaction, a portion of the DNA sample was taken and used to transform Escherichia coli. Typically, 16 Tn-inserted clones were picked up for each cDNA clone. With respect to the plasmid DNAs of clones thus obtained, the full-length cDNA sequences were determined in the same manner as in Example 5, by using Primer N (SEQ ID NO:166) and Primer S (SEQ ID NO:167) as primers.

(3) Novel full-length genes exhibiting a shear stress-dependent increase of expression

[0396] Using the sequence of A4RS-011 obtained from the subtraction library in Example 3 as a query, the cDNA sequences obtained in step (2) were searched by means of BLAST program [Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schaffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman, Nucleic Acids Res., 25, 3389-3402(1997)]. As a result, the sequence of A4RS-011 was identical with C-KAT07969 (SEQ ID NO:168). Among the ORFs of this cDNA sequence, the longest translated amino acid sequence was regarded as the amino acid sequence (121-1062; SEQ ID NO:169) encoded by the cDNA sequence of C-KAT07969. This amino acid sequence does not show substantial homology with other known proteins. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in panel 56 of FIG. 2.

[0397] Using the sequence of A4RS-604 obtained from the subtraction library in Example 3 as a query, the cDNA sequences obtained in step (2) were searched by means of BLAST program. As a result, the sequence of A4RS-604 was identical with the sequence of C-ADKA02341 (SEQ ID NO:170). This sequence is identical with a portion of the sequence of H. sapiens mRNA for myosin-I beta [Accession: X98507]. Among the ORFs of this cDNA sequence, the longest translated amino acid sequence was regarded as the amino acid sequence (SEQ ID NO:171) encoded by the cDNA sequence of C-ADKA02341. Its Northern blots exhibiting a shear stress-dependent increase of expression are shown in panel 64 of FIG. 2 and panel 18 of FIG. 4.

[0398] Using the sequence of A4RS-619 obtained from the subtraction library in Example 3 as a query, the cDNA sequences obtained in step (2) were searched by means of BLAST program. As a result, the sequence of A4RS-619 was identical with the sequence of C-hep01279 (SEQ ID NO:172). Among the ORFs of this cDNA sequence, the longest translated amino acid sequence was regarded as the amino acid sequence (SEQ ID NO:173) encoded by the cDNA sequence of C-hep01279. This amino acid sequence does not show substantial homology with other known proteins. Its Northern blot exhibiting a shear stress-dependent increase of expression is shown in panel 66 of FIG. 2.

Example 8

Detection of the apoptosis-suppressing activity of A4RS-041

[0399] In order to investigate the function of genes exhibiting a shear stress-dependent increase of expression which were obtained from the subtraction library, the following experiments were carried out with respect to a gene of unknown function, A4RS-041, having homology with the gene LFG capable of suppressing Fas-mediated apoptosis.

(1) Construction of a recombinant virus vector

[0400] Using a plasmid having the full-length A4RS-041 (SEQ ID NO:7) as a template, the part of the cDNA sequence which encodes the protein of A4RS-041 was specifically amplified by PCR. That is, in a PCR tube, 20 ng of the template plasmid DNA, 25 pmol of a 5'-terminal sense primer having the HindIII site added thereto (SEQ ID NO: 174), 25 pmol of a 3'-terminal antisense primer having the ClaI site added thereto (SEQ ID NO: 175), 5 µl of 10 x reaction buffer (attached to the enzyme), 5 µl of a 2 mM dNTP solution, and 0.5 µl of KOD DNA polymerase (2.5 units/µl; manufactured by Toyobo Co, Ltd.) were mixed, and sterilized water was added thereto so as to make a volume of 50 µl. This mixture was heated at 98°C for 15 seconds, at 65°C for 2 seconds, and at 74°C for 30 seconds. This cycle was repeated 25 times to amplify the cDNA. The resulting amplified fragment of the full-length A4RS-041 was purified by cleaving its ends with HindIII and ClaI, and ligated to virus vector pCLNCX (manufactured by IMGENEX) which had previously been cleaved with HindIII and ClaI. As a result, there was constructed a recombinant virus vector pCLNC041 with which the expression of A4RS-041 is induced by CMV promoter. With respect to the resulting recombinant virus vector pCLNC041, the nucleotide sequence of its inserted fragment part was determined. Thus, it was confirmed that no nucleotide substitution was caused by PCR. As a control, pCLNCGFP was constructed by inserting EFGP (enhanced green fluorescent protein; manufactured by Clontech) into the HindIII and ClaI sites of pCLNCX in the same manner.

(2) Preparation of HeLa cells expressing A4RS-041 to be highly and stably

[0401] Recombinant viruses were produced by introducing each of the recombinant virus vectors constructed in step (1) into 293 cells for virus production. For the transfection of 293 cells with pCLNC041 or pCLNCGFP, a TransFast (manufactured by Promega) was used. The procedure therefor was carried out according to the attached manual. The procedures for virus production and for the infection of HeLa cells were carried out according to the manual attached to the virus vector (manufactured by IMGENEX) used.

[0402] Two days after infection, 300 µg/ml of G418 (manufactured by life Technologies) was added to the HeLa cells and the incubation was continued, so that uninfected cells were selectively eliminated. According to this procedure, there were obtained transformants expressing A4RS-041 or GFP to be highly and stably.

(3) Detection of an apoptosis-suppressing activity

[0403] Apoptosis was induced by adding 100 ng/ml of anti-Fas monoclonal antibody CH-11 (manufactured by MBL) to the stable transformants of HeLa cells obtained in step (2) (i.e., the stable transformants of HeLa cells expressing the expression of A4RS-041 or GFP as a control). Twenty-four (24), 36 and 48 hours after the start of induction, the survival rate of the cells was measured by staining with trypan blue. For this purpose, the survival rate was measured for both suspended cells and adhering cells. All experiments were carried out in duplicate, and averages and standard deviations were obtained. The results are shown in FIG. 6A. Moreover, when the antibody concentration was altered to 10, 50, 100 and 500 ng/ml, the survival rate after 36 hours was measured. The results are shown in FIG. 6B. In the HeLa cells having A4RS-041 introduced thereinto (represented by ● in FIG. 6), a significant increase in survival rate was observed at all points as compared with the HeLa cells having GFP (control) introduced thereinto (represented by ■ in FIG. 6). Thus, it has been found that, at least in HeLa cells, A4RS-041 has an activity for suppressing Fas-mediated apoptosis.

Example 9Analysis of the distribution of expression of A4RS-041

[0404] With respect to A4RS-041 that was found to have an apoptosis-suppressing activity in Example 8, the following experiments were carried out in order to examine its sites of expression in human tissues.

(1) Analysis of the expression of A4RS-041 in human normal tissues

[0405] Using primers specific for A4RS-041 (SEQ ID NO:176,177) and a PCR DIG Labeling Mix (manufactured by Boehringer Mannheim), a template comprising the A4RS-041-containing plasmid obtained in Example 2 was subjected to PCR. Thus, a DIG-labeled A4RS-041 specific fragment was prepared. Using this DNA fragment as a probe, hybridization was carried out with a Human Multiple Tissue Northern Blot (manufactured by Clontech) on which RNAs derived from 8 human tissues had been blotted. After washing, chemiluminescence signals were detected using a DIG luminescence detection kit (manufactured by Boehringer Mannheim). The procedure therefor was carried out according to the manual attached to the kit. As shown in panel A of FIG. 7, signals specific for A4RS-041 were detected in the vicinity of about 2.5 kb. In Lanes 1 to 8, 2 µg each of poly(A)⁺ RNAs derived from spleen, kidney, skeletal muscle, liver, lung, placenta, brain and heart had been electrophoresed. Although signals were observed in all lanes, the signal in lane 7 (brain) was weak. Thus, it has been found that the expression of A4RS-041 is relatively low in the brain. On the other hand, it has been reported that the expression of LFG is very high in the brain and low in the periphery [Proc. Natl. Acad. Sci. USA, 22, 12673-12678(1999)]. This suggests that A4RS-041 and LFG function tissue-specifically.

(2) Investigation on the expression of A4RS-041 and LFG in human vascular endothelial cells and brain

[0406] Using a template comprising 1 µg of the HUVEC (having no shear stress applied thereto)-derived poly(A)⁺ RNA obtained in Example 2 or 1 µg of human brain-derived poly(A)⁺ RNA (manufactured by Clontech), single-stranded cDNA was synthesized using a Superscript Pre amplification System (manufactured by Life Technologies). The procedure therefor was carried out according to the manual attached to the kit. The finally obtained cDNA solution was diluted to 5 ml and used for PCR. Using these cDNAs as templates, PCR was carried out using primers specific for A4RS-041 (SEQ ID NO:176,177), LFG (SEQ ID NO:178,179) and G3PDH (SEQ ID NO:180,181). The reaction mixture contained 5 µl of a cDNA solution, 2 µl of 10 x reaction buffer (attached to the enzyme), 1.6 µl of a 2.5 mM dNTP solution, 1 µl of dimethyl sulfoxide, 10 pmol each of sense and antisense primers, and 0.1 µl of GeneTaq DNA polymerase (5 units/µl; manufactured by Nippon Gene Co., Ltd.), and sterilized water was added thereto so as to make a total

volume of 20 µl. After the template and the primers were denatured by heating at 94°C for 1 minute, a cycle comprising heating at 94°C for 1 minute, at 60°C for 1 minute, and at 72°C for 1 minute was repeated. The number of cycles was 33 for A4RS-041 and LFG, and 24 for G3PDH. The reaction mixture was kept at 72°C for 10 minutes and then cooled to 4°C. One-half of the resulting PCR product was subjected to 1.8% agarose electrophoresis. The results are shown in panel B of FIG. 7. In lane 1, a 100 bp ladder (manufactured by Life Technologies) was electrophoresed as a size marker. Lanes 2, 4 and 6 show the PCR products obtained with HUVEC-derived cDNA, and Lanes 3, 5 and 7 show the PCR products obtained with human brain-derived cDNA. Moreover, lanes 2 and 3 show the PCR products obtained with A4RS-041-specific primers, lanes 4 and 5 show the PCR products obtained with LFG-specific primers, and lanes 6 and 7 show the PCR products obtained with G3PDH-specific primers.

[0407] The band of A4RS-041 is amplified in both HUVECs (lane 2) and the brain (lane 3), indicating that A4RS-041 is expressed in both of them. Its expression level in the brain tends to be lower than in HUVECs. On the other hand, LFG is very strongly expressed in the brain (lane 5), but the band of LFG is not amplified at all in HUVECs (lane 4), and this indicates that LFG is not expressed in HUVECs.

[0408] From the above-described results, it is believed that the factor involved in the suppression of apoptosis in endothelial cells is not LFG but A4RS-041.

[0409] The homology between the amino acid sequences of A4RS-041 and LFG (human-derived) is shown in FIG. 8. They are judged to be homologous proteins having 48.9% (152/311) identity. However, it has been found that a portion corresponding to about one-third on the N-terminal side has considerably low homology.

FREE-TEXT-FOR SEQUENCE LISTING

[0410]

SEQ ID NO:159 - Description of artificial sequence: Artificial synthetic primer sequence

SEQ ID NO:160 - Description of artificial sequence: Artificial synthetic primer sequence

SEQ ID NO:161 - Description of artificial sequence: Artificial synthetic primer sequence

SEQ ID NO:162 - Description of artificial sequence: Oligo-cap linker sequence

SEQ ID NO:163 - Description of artificial sequence: Oligo-dT primer sequence

SEQ ID NO:164 - Description of artificial sequence: Artificial synthetic primer sequence

SEQ ID NO:165 - Description of artificial sequence: Artificial synthetic primer sequence

SEQ ID NO:166 - Description of artificial sequence: Artificial synthetic primer sequence

SEQ ID NO:167 - Description of artificial sequence: Artificial synthetic primer sequence

SEQ ID NO:174 - Description of artificial sequence: Synthetic DNA

SEQ ID NO:175 - Description of artificial sequence: Synthetic DNA

SEQ ID NO:176 - Description of artificial sequence: Synthetic DNA

SEQ ID NO:177 - Description of artificial sequence: Synthetic DNA

SEQ ID NO:178 - Description of artificial sequence: Synthetic DNA

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SEQ ID NO:180 - Description of artificial sequence: Synthetic DNA

SEQ ID NO:181 - Description of artificial sequence: Synthetic DNA

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Met Asn Gly Pro Glu Asp Leu Pro Lys Ser Tyr

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15		Ala	Lys	Glu	Ala	Ala	Gln	Tyr	Gly	Lys	Lys	Val	Met	Val	Leu	Asp	Phe	
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50		Lys	Val	Val	Tyr	Glu	Asn	Ala	Tyr	Gly	Gln	Phe	Ile	Gly	Pro	His	Arg	
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	Tyr Cys Pro Gly Lys Thr Leu Val Val Gly Ala Ser Tyr Val Ala Leu	
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	Glu Cys Ala Gly Phe Leu Ala Gly Ile Gly Leu Gly Val Thr Val Met	
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35	Val Arg Ser Ile Leu Leu Arg Gly Phe Asp Gln Asp Met Ala Asn Lys	
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	320 325 330	
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	Glu Glu Asn Ile Glu Val Tyr His Ser Tyr Phe Trp Pro Leu Glu Trp	
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	Asn Lys Gly Lys Glu Lys Ile Tyr Ser Ala Glu Ser Phe Leu Ile Ala			
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	Thr Gly Glu Arg Pro Arg Tyr Leu Gly Ile Pro Gly Asp Lys Glu Tyr			
	165	170	175	
45	Cys Ile Ser Ser Asp Asp Leu Phe Ser Leu Pro Tyr Cys Pro Gly Lys			
	180	185	190	
50	Thr Leu Val Val Gly Ala Ser Tyr Val Ala Leu Glu Cys Ala Gly Phe			
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	Glu Gln Ile Glu Ala Gly Thr Pro Gly Arg Leu Arg Val Val Ala Gln	
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	Glu Glu Gln Thr Asn Val Pro Tyr Ile Tyr Ala Ile Gly Asp Ile Leu	
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	Glu Asp Lys Val Glu Leu Thr Pro Val Ala Ile Gln Ala Gly Arg Leu	
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	Leu Ser Glu Glu Lys Ala Val Glu Lys Phe Gly Glu Glu Asn Ile Glu	
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	Val Tyr His Ser Tyr Phe Trp Pro Leu Glu Trp Thr Ile Pro Ser Arg	
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 45 tgg ccg cga ccc ccc gcc ccg ggc ccg ccc ccg ccg ctc ccg ctg 98
 Trp Pro Arg Pro Pro Ala Pro Gly Pro Pro Pro Pro Pro Leu Pro Leu
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 50 ctg ctc ctg ctc ctg gcc ggg ctg ctg ggc ggc gcg ggc gcg cag tac 146
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 55 35 40 45

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tcc agc gac cgg tgc agc tgg aag ggg agc ggg ctg acg cac gag gca 194
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 gtg gag tgg atg tac cca aca ggt gct ctc atc gtt aac ctg cgg ccc 290
 15 Val Glu Trp Met Tyr Pro Thr Gly Ala Leu Ile Val Asn Leu Arg Pro
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 25 100 105 110
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 15 gcc atc cac ctg cgc gtg agc aga ctc tat cgg cag aaa agc agg gtc 722
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 40 35 40 45
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 55 100 105 110

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	180 185 190
25	Asp Thr Glu Val Leu Leu Ala Val Cys Thr Ser Asp Phe Ala Val Arg
	195 200 205
30	Gly Ser Ile Gln Gln Val Thr His Glu Pro Glu Arg Gln Asp Ser Ala
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	Ile His Leu Arg Val Ser Arg Leu Tyr Arg Gln Lys Ser Arg Val Phe
	225 230 235 240
35	Glu Pro Val Pro Glu Gly Asp Gly His Trp Gln Gly Arg Val Arg Thr
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25

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Arg Gln Thr Gly Ile Val Leu Asn Arg Pro Val Leu Arg Gly Glu Asp

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ggg gac aaa gcc gct cca cct ccc atg tgg gca cag ctc cct gga att 249

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75

80

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	Arg Gln Glu Glu Met Asn Ser Gln Gln Glu Glu Glu Met Glu Thr	
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20	gat gct cgc tgc tcc ctg ggc cag tca gcg tca gag act gag gag gac	921
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	aca gtg tcc gla tct aaa aag gag aaa aac cgg aag cgt agg aac cga	969
	Thr Val Ser Val Ser Lys Lys Glu Lys Asn Arg Lys Arg Arg Asn Arg	
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	aag aag aag aaa aag ccc cag cgg gtg cga ggg gtg tcc tct gag agc	1017
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	Ser Gly Asp Arg Glu Lys Asp Ser Thr Arg Ser Arg Gly Ser Asp Ser	
	325 330 335	
45	cca gca gct gat gtt gag att gag tat gtg act gaa gaa cct gaa att	1113
	Pro Ala Ala Asp Val Glu Ile Glu Tyr Val Thr Glu Glu Pro Glu Ile	
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	Tyr Glu Pro Asn Phe Ile Phe Phe Lys Arg Ile Phe Glu Ala Phe Lys	
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 405 410 415

20 aag cca gaa gcc ccc aag ctg tcc aag aag aag ttg cgc cga atg aac 1353
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 420 425 430 435

25 cgc ttc act gtg gct gaa ctc aag cag ctg gtg gct cgg ccc gat gtc 1401
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 440 445 450

30 gtg gag atg cac gat gtg aca gcg cag gac cct aag ctc ttg gtt cac 1449
 Val Glu Met His Asp Val Thr Ala Gln Asp Pro Lys Leu Leu Val His
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 Lys Arg Lys Tyr Leu Gln Gly Lys Arg Gly Ile Glu Lys Pro Pro Phe
 485 490 495

45 gag ctg cca gac ttc alc aaa cgc aca ggc alc cag gag atg cga gag 1593
 Glu Leu Pro Asp Phe Ile Lys Arg Thr Gly Ile Gln Glu Met Arg Glu

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	Glu Lys Val Arg Pro Lys Met Gly Lys Ile Asp Ile Asp Tyr Gln Lys				
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	ctg cat gat gcc ttc ttc aag tgg cag acc aag cca aag ctg acc atc				1737
20	Leu His Asp Ala Phe Phe Lys Trp Gln Thr Lys Pro Lys Leu Thr Ile				
	550	555	560		
25	cat ggg gac ctg tac tat gag ggg aag gag ttc gag aca cga ctg aag				1785
	His Gly Asp Leu Tyr Tyr Glu Gly Lys Glu Phe Glu Thr Arg Leu Lys				
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	Glu Lys Lys Pro Gly Asp Leu Ser Asp Glu Leu Arg Ile Ser Leu Gly				
	580	585	590	595	
35	atg cca gta gga cca aat gcc cac aag glc cct ccc cca tgg ctg att				1881
	Met Pro Val Gly Pro Asn Ala His Lys Val Pro Pro Pro Trp Leu Ile				
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	gcc atg cag cga tat gga cca ccc cca tcg tat ccc aac ctg aaa atc				1929
	Ala Met Gln Arg Tyr Gly Pro Pro Pro Ser Tyr Pro Asn Leu Lys Ile				
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50	Pro Gly Leu Asn Ser Pro Ile Pro Glu Ser Cys Ser Phe Gly Tyr His				
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55	gct ggt ggc tgg ggc aaa cct cca gtg gat gag act ggg aaa ccg ctg				2025
	Ala Gly Gly Trp Gly Lys Pro Pro Val Asp Glu Thr Gly Lys Pro Leu				

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 Gly Asp His Ser Leu Lys Glu His Glu Leu Leu Glu Gln Gln Lys Arg
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10	Lys Glu Ser Arg Gln Glu Glu Met Asn Ser Gln Gln Glu Glu Glu Glu			
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15	Met Glu Thr Asp Ala Arg Ser Ser Leu Gly Gln Ser Ala Ser Glu Thr			
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	Glu Glu Asp Thr Val Ser Val Ser Lys Lys Glu Lys Asn Arg Lys Arg			
20		290	295	300
	Arg Asn Arg Lys Lys Lys Lys Lys Pro Gln Arg Val Arg Gly Val Ser			
25	305	310	315	320
	Ser Glu Ser Ser Gly Asp Arg Glu Lys Asp Ser Thr Arg Ser Arg Gly			
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30	Ser Asp Ser Pro Ala Ala Asp Val Glu Ile Glu Tyr Val Thr Glu Glu			
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	Ala Phe Lys Leu Thr Asp Asp Val Lys Lys Glu Lys Glu Lys Glu Pro			
40		370	375	380
	Glu Lys Leu Asp Lys Leu Glu Asn Ser Ala Ala Pro Lys Lys Lys Gly			
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	Phe Glu Glu Glu His Lys Asp Ser Asp Asp Asp Ser Ser Asp Asp Glu			
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50	Gln Glu Lys Lys Pro Glu Ala Pro Lys Leu Ser Lys Lys Lys Leu Arg			
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10	Leu Val His Leu Lys Ala Thr Arg Asn Ser Val Pro Val Pro Arg His			
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	Trp Cys Phe Lys Arg Lys Tyr Leu Gln Gly Lys Arg Gly Ile Glu Lys			
15	485	490	495	
	Pro Pro Phe Glu Leu Pro Asp Phe Ile Lys Arg Thr Gly Ile Gln Glu			
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	Met Arg Glu Ala Leu Gln Glu Lys Glu Glu Gln Lys Thr Met Lys Ser			
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25	Lys Met Arg Glu Lys Val Arg Pro Lys Met Gly Lys Ile Asp Ile Asp			
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30	Tyr Gln Lys Leu His Asp Ala Phe Phe Lys Trp Gln Thr Lys Pro Lys			
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	Leu Thr Ile His Gly Asp Leu Tyr Tyr Glu Gly Lys Glu Phe Glu Thr			
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	Arg Leu Lys Glu Lys Lys Pro Gly Asp Leu Ser Asp Glu Leu Arg Ile			
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	Ser Leu Gly Met Pro Val Gly Pro Asn Ala His Lys Val Pro Pro Pro			
	595	600	605	
45	Trp Leu Ile Ala Met Gln Arg Tyr Gly Pro Pro Pro Ser Tyr Pro Asn			
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50	Leu Lys Ile Pro Gly Leu Asn Ser Pro Ile Pro Glu Ser Cys Ser Phe			
	625	630	635	640
	Gly Tyr His Ala Gly Gly Trp Gly Lys Pro Pro Val Asp Glu Thr Gly			
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 10 Thr Lys Thr Glu Glu Glu Glu Ile Asp Arg Thr Pro Trp Gly Glu Leu
 675 680 685
 15 Glu Pro Ser Asp Glu Glu Ser Ser Glu Glu Glu Glu Glu Glu Ser
 690 695 700
 20 Asp Glu Asp Lys Pro Asp Glu Thr Gly Phe Ile Thr Pro Ala Asp Ser
 705 710 715 720
 25 Gly Leu Ile Thr Pro Gly Gly Phe Ser Ser Val Pro Ala Gly Met Glu
 725 730 735
 30 Thr Pro Glu Leu Ile Glu Leu Arg Lys Lys Lys Ile Glu Glu Ala Met
 740 745 750
 35 Asp Gly Ser Glu Thr Pro Gln Leu Phe Thr Val Leu Pro Glu Lys Arg
 755 760 765
 40 Thr Ala Thr Val Gly Gly Ala Met Met Gly Ser Thr His Ile Tyr Asp
 770 775 780
 45 Met Ser Thr Val Met Ser Arg Lys Gly Pro Ala Pro Glu Leu Gln Gly
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ctggccccg gaggctcttg ccagcttgac agtgttcttg gcactgctca aaggccccag 180

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Met Ser Asn Pro Ser Ala Pro

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cca cca tat gaa gac cgc aac ccc ctg tac cca ggc cct ccg ccc cct 282

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35	165	170	175
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	Thr Gly Phe Asn Tyr Gln Asn Glu Asp Glu Lys Val Thr Leu Ser Phe	
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	Thr Asp Ala Arg Arg Ala Phe Pro Cys Trp Asp Glu Pro Ala Ile Lys	
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25	Gly Lys Phe Ala Leu Glu Val Ala Ala Lys Thr Leu Pro Phe Tyr Lys				
	235	240	245		
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765 770 775
cat ggt agg aaa gct gct tgg aaa ttc ata aag gac aac tgg gaa gaa 2464
15 His Gly Arg Lys Ala Ala Trp Lys Phe Ile Lys Asp Asn Trp Glu Glu
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Ile Val Met Asn Cys Ala Asp Ile Asp Ile Ile Thr Ala Ser Tyr Ala
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Pro Glu Gly Asp Glu Glu Ile His Ala Thr Gly Phe Asn Tyr Gln Asn
25 65 70 75 80
Glu Asp Glu Lys Val Thr Leu Ser Phe Pro Ser Thr Leu Gln Thr Gly
85 90 95
30 Thr Gly Thr Leu Lys Ile Asp Phe Val Gly Glu Leu Asn Asp Lys Met
100 105 110
Lys Gly Phe Tyr Arg Ser Lys Tyr Thr Thr Pro Ser Gly Glu Val Arg
35 115 120 125
Tyr Ala Ala Val Thr Gln Phe Glu Ala Thr Asp Ala Arg Arg Ala Phe
40 130 135 140
Pro Cys Trp Asp Glu Pro Ala Ile Lys Ala Thr Phe Asp Ile Ser Leu
45 145 150 155 160
Val Val Pro Lys Asp Arg Val Ala Leu Ser Asn Met Asn Val Ile Asp
165 170 175
50 Arg Lys Pro Tyr Pro Asp Asp Glu Asn Leu Val Glu Val Lys Phe Ala
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55 Arg Thr Pro Val Met Ser Thr Tyr Leu Val Ala Phe Val Val Gly Glu

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5	Tyr Asp Phe Val Glu Thr Arg Ser Lys Asp Gly Val Cys Val Arg Val		
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40	Val Lys Pro Asp Gln Trp Val Lys Leu Asn Leu Gly Thr Val Gly Phe			
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50	Ile Arg Asp Leu Ser Leu Pro Pro Val Asp Arg Leu Gly Leu Gln Asn			
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65	Ser Asp Leu Ser Cys Asn Leu Gly Ile Leu Ser Thr Leu Leu Ser His			
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 Pro Ile Gly Glu Arg Leu Gly Trp Asp Pro Lys Pro Gly Glu Gly His
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 15 Gly His Lys Ala Thr Leu Glu Glu Ala Arg Arg Arg Phe Lys Asp His
 675 680 685
 20 Val Glu Gly Lys Gln Ile Leu Ser Ala Asp Leu Arg Ser Pro Val Tyr
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 Lys Leu His Lys Gln Ala Asp Met Gln Glu Glu Lys Asn Arg Ile Glu
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 770 775 780
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Met Glu Thr Pro Ser Gln Arg Arg Ala Thr Arg Ser

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-15

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60

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80

85

90

gac tca gta gcc aag gag cgc gcc cgc ctg cag ctg gag ctg agc aaa 458

Asp Ser Val Ala Lys Glu Arg Ala Arg Leu Gln Leu Glu Leu Ser Lys

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	Gly Ser Val Thr Lys Lys Arg Lys Leu Glu Ser Thr Glu Ser Arg Ser			
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20	agc ttc tca cag cac gca cgc act agc ggg cgc gtg gcc gtg gag gag	1466		
	Ser Phe Ser Gln His Ala Arg Thr Ser Gly Arg Val Ala Val Glu Glu			
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	ccc ttg ctg act tac cgg ttc cca cca aag ttc acc ctg aag gct ggg	1610		
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45	cag gtg gtg acg atc tgg gct gca gga gct ggg gcc acc cac agc ccc	1658		
	Gln Val Val Thr Ile Trp Ala Ala Gly Ala Gly Ala Thr His Ser Pro			
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50	cct acc gac ctg gtg tgg aag gca cag aac acc tgg ggc tgc ggg aac	1706		
	Pro Thr Asp Leu Val Trp Lys Ala Gln Asn Thr Trp Gly Cys Gly Asn			
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55	agc ctg cgt acg gct ctc atc aac tcc act ggg gaa gaa gtg gcc atg	1754		

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	Gln Gln Gln Leu Asp Glu Tyr Gln Glu Leu Leu Asp Ile Lys Leu Ala			
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25	Glu Arg Leu Arg Leu Ser Pro Ser Pro Thr Ser Gln Arg Ser Arg Gly			
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	Arg Ala Ser Ser His Ser Ser Gln Thr Gln Gly Gly Gly Ser Val Thr			
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	Lys Lys Arg Lys Leu Glu Ser Thr Glu Ser Arg Ser Ser Phe Ser Gln			
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	His Ala Arg Thr Ser Gly Arg Val Ala Val Glu Glu Val Asp Glu Glu			
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40	Gly Lys Phe Val Arg Leu Arg Asn Lys Ser Asn Glu Asp Gln Ser Met			
	450	455	460	
45	Gly Asn Trp Gln Ile Lys Arg Gln Asn Gly Asp Asp Pro Leu Leu Thr			
	465	470	475	480
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	Ile Trp Ala Ala Gly Ala Gly Ala Thr His Ser Pro Pro Thr Asp Leu			
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Val Trp Lys Ala Gln Asn Thr Trp Gly Cys Gly Asn Ser Leu Arg Thr
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Ala Leu Ile Asn Ser Thr Gly Glu Glu Val Ala Met Arg Lys Leu Val
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Gly Ile Val Pro Gly Asn Arg Val Lys Leu Leu Ile Gly Pro Met Gln

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Glu Thr Ala Ser Ser His Glu Gln Pro Ala Ser Gly Leu Met Gln Gln

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 40 Lys Glu Leu Leu Glu Lys Glu Asn Ile Met Lys Gln Asn Lys Met Gln
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	Leu Pro Thr Thr Asn Ser Gly Val Ser Ala Gln Asp Arg Gln Leu Leu			
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	tgc ttc tac tat gac caa tgt gag acc cat ttc att tcc ctt ctc aac	2335		
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25	gcc att gac gca ctc ttc agt tgt gtc agc tca gcc cag ccc ccg cga	2383		
	Ala Ile Asp Ala Leu Phe Ser Cys Val Ser Ser Ala Gln Pro Pro Arg			
	725	730	735	740
30	atc ttc gtg gca cac agc aag ttt gtc atc ctc agt gca cac aaa ctg	2431		
	Ile Phe Val Ala His Ser Lys Phe Val Ile Leu Ser Ala His Lys Leu			
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35	gtg ttc att gga gac acg ctg aca cgg cag gtg act gcc cag gac att	2479		
	Val Phe Ile Gly Asp Thr Leu Thr Arg Gln Val Thr Ala Gln Asp Ile			
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	cgc aac aaa gtc atg aac tcc agc aac cag ctc tgc gag cag ctc aag	2527		
	Arg Asn Lys Val Met Asn Ser Ser Asn Gln Leu Cys Glu Gln Leu Lys			
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55	acg gcc ctg cag gaa atg gtg cac caa gtg aca gac ctt tct aga aat	2623		
	Thr Ala Leu Gln Glu Met Val His Gln Val Thr Asp Leu Ser Arg Asn			

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35 40 45

His Gly Arg Gln Gly Ile Val Pro Gly Asn Arg Val Lys Leu Leu Ile

50 55 60

Gly Pro Met Gln Glu Thr Ala Ser Ser His Glu Gln Pro Ala Ser Gly

65 70 75 80

Leu Met Gln Gln Thr Phe Gly Gln Gln Lys Leu Tyr Gln Val Pro Asn

85 90 95

Pro Gln Ala Ala Pro Arg Asp Thr Ile Tyr Gln Val Pro Pro Ser Tyr

100 105 110

Gln Asn Gln Gly Ile Tyr Gln Val Pro Thr Gly His Gly Thr Gln Glu

115 120 125

Gln Glu Val Tyr Gln Val Pro Pro Ser Val Gln Arg Ser Ile Gly Gly

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Thr Ser Gly Pro His Val Gly Lys Lys Val Ile Thr Pro Val Arg Thr

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Gly His Gly Tyr Val Tyr Glu Tyr Pro Ser Arg Tyr Gln Lys Asp Val

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Tyr Asp Ile Pro Pro Ser His Thr Thr Gln Gly Val Tyr Asp Ile Pro

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	Tyr Asp Phe Pro Pro Pro Met Arg Gln Ala Gly Arg Pro Asp Leu Arg		240
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25	Lys Asp Leu His Val Lys Tyr Asn Cys Asp Ile Pro Gly Ala Ala Glu		
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	Pro Val Ala Arg Arg His Gln Ser Leu Ser Pro Asn His Pro Pro Pro		
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	Gln Leu Gly Gln Ser Val Gly Ser Gln Asn Asp Ala Tyr Asp Val Pro		
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	Arg Gly Val Gln Phe Leu Glu Pro Pro Ala Glu Thr Ser Glu Lys Ala		320
	325	330	335
40	Asn Pro Gln Glu Arg Asp Gly Val Tyr Asp Val Pro Leu His Asn Pro		
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45	Pro Asp Ala Lys Gly Ser Arg Asp Leu Val Asp Gly Ile Asn Arg Leu		
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50	Ser Phe Ser Ser Thr Gly Ser Thr Arg Ser Asn Met Ser Thr Ser Ser		
	370	375	380
	Thr Ser Ser Lys Glu Ser Ser Leu Ser Ala Ser Pro Ala Gln Asp Lys		
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			400

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	Arg	Leu	Phe	Leu	Asp	Pro	Asp	Thr	Ala	Ile	Glu	Arg	Leu	Gln	Arg	Leu	
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10						420					425					430	
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						435					440					445	
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	Leu	His	Asn	Lys	Met	Lys	Arg	Glu	Leu	Gln	Arg	Val	Glu	Asp	Ser	His	
25						485					490					495	
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450 455 460

²⁰ Phe Val Lys Gly Ala Val Ala Asn Ala Ala Cys Leu Pro Glu Leu Ile

465 470 475 480

Leu His Asn Lys Met Lys Arg Glu Leu Gln Arg Val Glu Asp Ser His

485 · **490** **495**

Gln Ile Leu Ser Gln Thr Ser His Asp Leu Asn Glu Cys Ser Trp Ser

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530 535 540

40 Leu Thr Thr Thr Ile Asn Thr Asn Ala Glu Ala Leu Phe Arg Pro Gly

545 550 555 560

45 Pro Gly Ser Leu His Leu Lys Asn Gly Pro Glu Ser Ile Met Asn Ser

565 570 575

Thr Glu Tyr Pro His Gly Gly Ser Gln Gly Gln Leu Leu His Pro Gly

580

Asp His Lys Ala Gln Ala His Asn Lys Ala Leu Pro Pro Gly Leu Ser

55

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 5 Trp Met Asp Asp Tyr Asp Tyr Val His Leu Gln Gly Lys Glu Glu Phe
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 10 Glu Arg Gln Gln Lys Glu Leu Leu Glu Lys Glu Asn Ile Met Lys Gln
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 690 - 695 700
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	Phe Gln Val Ser Leu Ser Ser Ser Met Ser Val Ser Glu Leu Lys Ala			
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45	Val His Pro Ser Gly Val Ala Leu Gln Asp Arg Val Pro Leu Ala Ser			
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 15 Val Ser Gly Leu Glu Gly Val Gln Asp Asp Leu Phe Trp Leu Thr Phe
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 10 Arg Val Pro Leu Ala Ser Gln Gly Leu Gly Pro Gly Ser Thr Val Leu
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 15 Leu Val Val Asp Lys Cys Asp Glu Pro Leu Ser Ile Leu Val Arg Asn
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10	Ala	Leu	Leu	Leu	Ala	Ala	Ala	Gly	Thr	Ala	Val	Gly	Asp Arg Cys Glu
		15			20				25				
	aga	aac	gag	ttc	cag	tgc	caa	gac	ggg	aaa	tgc	atc	tcc tac aag tgg 145
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	Glu	Thr	Cys	Leu	Ser	Val	Thr	Cys	Lys	Ser	Gly	Asp	Phe Ser Cys Gly
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35	Gly	Arg	Val	Asn	Arg	Cys	Ile	Pro	Gln	Phe	Trp	Arg	Cys Asp Gly Gln
					80				85				90
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40	Val	Asp	Cys	Asp	Asn	Gly	Ser	Asp	Glu	Gln	Gly	Cys	Pro Pro Lys Thr
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45	tgc	tcc	cag	gac	gag	ttt	cgc	tgc	cac	gat	ggg	aag	tgc atc tct cgg 385
	Cys	Ser	Gln	Asp	Glu	Phe	Arg	Cys	His	Asp	Gly	Lys	Cys Ile Ser Arg
					110				115				120
50	cag	ttc	gtc	tgt	gac	tca	gac	cgg	gac	tgc	tig	gac	ggc tca gac gag 433
	Gln	Phe	Val	Cys	Asp	Ser	Asp	Arg	Asp	Cys	Leu	Asp	Gly Ser Asp Glu
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 10 Ser Ser Thr Cys Ile Pro Gln Leu Trp Ala Cys Asp Asn Asp Pro Asp
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 15 Cys Glu Asp Gly Ser Asp Glu Trp Pro Gln Arg Cys Arg Gly Leu Tyr
 175 180 185
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 255 260 265
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 45 Gly Cys Val Asn Val Thr Leu Cys Glu Gly Pro Asn Lys Phe Lys Cys
 270 275 280

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 15 gaa tgc ttg gac aac aac ggc ggc tgt tcc cac gtc tgc aat gac ctt 1009
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 20 320 325 330
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10	gac ctg tcc cag aga atg atc tgc agc acc cag ctt gac aga gcc cac			1393
	Asp Leu Ser Gln Arg Met Ile Cys Ser Thr Gln Leu Asp Arg Ala His			
15	445	450	455	460
	ggc gtc tct tcc tal gac acc gtc atc agc agg gac atc cag gcc ccc			1441
	Gly Val Ser Ser Tyr Asp Thr Val Ile Ser Arg Asp Ile Gln Ala Pro			
20		465	470	475
	gac ggg ctg gct gtg gac tgg atc cac agc aac atc tac tgg acc gac			1489
25	Asp Gly Leu Ala Val Asp Trp Ile His Ser Asn Ile Tyr Trp Thr Asp			
	480	485	490	
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	Ser Val Leu Gly Thr Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg			
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35	aaa acg tta ttc agg gag aac ggc tcc aag cca agg gcc atc gtg gtg			1585
	Lys Thr Leu Phe Arg Glu Asn Gly Ser Lys Pro Arg Ala Ile Val Val			
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40	gat cct gtt cat ggc ttc atg tac tgg act gac tgg gga act ccc gcc			1633
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	Lys Ile Lys Lys Gly Gly Leu Asn Gly Val Asp Ile Tyr Ser Leu Val			
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	ctg gcc cac ccc ttc tcc ttg gcc gtc ttt gag gac aaa gta ttt tgg			1873
20	Leu Ala His Pro Phe Ser Leu Ala Val Phe Glu Asp Lys Val Phe Trp			
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	aca gat atc atc aac gaa gcc att ttc agt gcc aac cgc ctc aca ggt			1921
25	Thr Asp Ile Ile Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly			
	625	630	635	
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	Ser Asp Val Asn Leu Leu Ala Glu Asn Leu Leu Ser Pro Glu Asp Met			
	640	645	650	
35	gtc ctc ttc cac aac ctc acc cag cca aga gga gtg aac tgg tgt gag			2017
	Val Leu Phe His Asn Leu Thr Gln Pro Arg Gly Val Asn Trp Cys Glu			
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 50 cag aag acc aca gag gat gag gtc cac att tgc cac aac cag gac ggc 2545
 Gln Lys Thr Thr Glu Asp Glu Val His Ile Cys His Asn Gln Asp Gly
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Tyr Ser Tyr Pro Ser Arg Gln Met Val Ser Leu Glu Asp Asp Val Ala

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45 <212> PRT

<213> Homo sapiens

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20	Arg Cys Ile Pro Gln Phe Trp Arg Cys Asp Gly Gln Val Asp Cys Asp		
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25	Asn Gly Ser Asp Glu Gln Gly Cys Pro Pro Lys Thr Cys Ser Gln Asp		
	100	105	110
30	Glu Phe Arg Cys His Asp Gly Lys Cys Ile Ser Arg Gln Phe Val Cys		
	115	120	125
35	Asp Ser Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala Ser Cys Pro		
	130	135	140
40	Val Leu Thr Cys Gly Pro Ala Ser Phe Gln Cys Asn Ser Ser Thr Cys		
	145	150	155
45	Ile Pro Gln Leu Trp Ala Cys Asp Asn Asp Pro Asp Cys Glu Asp Gly		
	165	170	175
50	Ser Asp Glu Trp Pro Gln Arg Cys Arg Gly Leu Tyr Val Phe Gln Gly		
	180	185	190
55	Asp Ser Ser Pro Cys Ser Ala Phe Glu Phe His Cys Leu Ser Gly Glu		
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	Cys Ile His Ser Ser Trp Arg Cys Asp Gly Gly Pro Asp Cys Lys Asp		
	210	215	220
	Lys Ser Asp Glu Glu Asn Cys Ala Val Ala Thr Cys Arg Pro Asp Glu		
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			240

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						260					265				270	
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40	Leu	Asp	Pro	His	Thr	Lys	Ala	Cys	Lys	Ala	Val	Gly	Ser	Ile	Ala	Tyr
						385					390				395	
	Leu	Phe	Phe	Thr	Asn	Arg	His	Glu	Val	Arg	Lys	Met	Thr	Leu	Asp	Arg
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	Ser	Glu	Tyr	Thr	Ser	Leu	Ile	Pro	Asn	Leu	Arg	Asn	Val	Val	Ala	Leu
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	Asp	Thr	Glu	Val	Ala	Ser	Asn	Arg	Ile	Tyr	Trp	Ser	Asp	Leu	Ser	Gln
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15	Thr Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Lys Thr Leu Phe
	500 505 510
	Arg Glu Asn Gly Ser Lys Pro Arg Ala Ile Val Val Asp Pro Val His
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	Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys
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	Gly Gly Leu Asn Gly Val Asp Ile Tyr Ser Leu Val Thr Glu Asn Ile
30	545 550 555 560
	Gln Trp Pro Asn Gly Ile Thr Leu Asp Leu Leu Ser Gly Arg Leu Tyr
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	Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Lys Arg Leu Ala His Pro
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	Phe Ser Leu Ala Val Phe Glu Asp Lys Val Phe Trp Thr Asp Ile Ile
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	Thr Gln Glu Thr Ser Thr Val Arg Leu Lys Val Ser Ser Thr Ala Val		720
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20	Arg Thr Gln His Thr Thr Thr Arg Pro Val Pro Asp Thr Ser Arg Leu		
	740	745	750
25	Pro Gly Ala Thr Pro Gly Leu Thr Thr Val Glu Ile Val Thr Met Ser		
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30	His Gln Ala Leu Gly Asp Val Ala Gly Arg Gly Asn Glu Lys Lys Pro		
	770	775	780
	Ser Ser Val Arg Ala Leu Ser Ile Val Leu Pro Ile Val Leu Leu Val		
35	785	790	795
	Phe Leu Cys Leu Gly Val Phe Leu Leu Trp Lys Asn Trp Arg Leu Lys		800
40	805	810	815
	Asn Ile Asn Ser Ile Asn Phe Asp Asn Pro Val Tyr Gln Lys Thr Thr		
	820	825	830
45	Glu Asp Glu Val His Ile Cys His Asn Gln Asp Gly Tyr Ser Tyr Pro		
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50	Ser Arg Gln Met Val Ser Leu Glu Asp Asp Val Ala		
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Met Leu Leu

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Leu Leu Leu Ser Ile Ile Val Leu His Val Ala Val Leu Val Leu Leu

5

10

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35

Gly His Ala Thr Asp Leu Trp Gln Asn Cys Ser Thr Ser Ser Ser Gly

35 40 45

Asn Val His His Cys Phe Ser Ser Ser Pro Asn Glu Trp Leu Gln Ser

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Val Gln Ala Thr Met Ile Leu Ser Ile Ile Phe Ser Ile Leu Ser Leu

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Phe Leu Phe Phe Cys Gln Leu Phe Thr Leu Thr Lys Gly Gly Arg Phe

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Tyr Ile Thr Gly Ile Phe Gln Ile Leu Ala Gly Leu Cys Val Met Ser

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	ccc ctg ggt gag gat gaa cag gat gac tgg ata gtg gtc agc cag ctc	341
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	90 95 100	
20	aga atc acc tcc ctg cag ctt tcc gac acg gga cag tac cag tgt ttg	389
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	Val Phe Leu Gly His Gln Thr Phe Val Ser Gln Pro Gly Tyr Val Gly	
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	Glu Pro Val Asp Leu Leu Trp Leu Gln Asp Ala Val Pro Leu Ala Thr	
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 55 330 335 340

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	Ser Glu Glu Leu Lys Glu Lys Leu Arg Asp Val Met Val Asp Arg His			
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30	atg gaa ggc cag ctg aac cag gac gac tcc atc ctg aag gtg gct gtg	1733		
	Met Glu Gly Gln Leu Asn Gln Asp Asp Ser Ile Leu Lys Val Ala Val			
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	Lys Thr Met Lys Ile Ala Ile Cys Thr Arg Ser Glu Leu Glu Asp Phe			
40	570	575	580	
	ctg agt gaa gcg gtc tgc atg aag gaa ttt gac cat ccc aac gtc atg	1829		
	Leu Ser Glu Ala Val Cys Met Lys Glu Phe Asp His Pro Asn Val Met			
45	585	590	595	
	agg ctg atc ggt gtc tgt ttc cag ggt tct gaa cga gag agc ttc cca	1877		
50	Arg Leu Ile Gly Val Cys Phe Gln Gly Ser Glu Arg Glu Ser Phe Pro			
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55	gca cct gtg gtc atc tta cct ttc atg aaa cat gga gac cta cac agc	1925		
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5	ttc ctc ctc tat tcc cgg ctc ggg ggc cag cca glg tac ctg ccc act	1973			
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	Gln Met Leu Val Lys Phe Met Ala Asp Ile Ala Ser Gly Met Glu Tyr				
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20	Leu Ser Thr Lys Arg Phe Ile His Arg Asp Leu Ala Ala Arg Asn Cys				
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25	atg ctg aat gag aac atg tcc glg tgt glg gcg gac ttc ggg ctc tcc	2117			
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	Lys Lys Ile Tyr Asn Gly Asp Tyr Tyr Arg Gln Gly Arg Ile Ala Lys				
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	atg cca gtc aag tgg att gcc att gag agt cta gct gac cgt gtc tac	2213			
	Met Pro Val Lys Trp Ile Ala Ile Glu Ser Leu Ala Asp Arg Val Tyr				
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	acc agc aag agc gat glg lgg tcc ttc ggg glg aca atg tgg gag att	2261			
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50	gcc aca aga ggc caa acc cca tat ccg ggc glg gag aac agc gag att	2309			
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 Gln Asp Arg Pro Ser Phe Thr Glu Leu Arg Glu Asp Leu Glu Asn Thr
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 aac atg gat gag ggt gga ggt tat cct gaa ccc cct gga gct gca gga 2549
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20 25 30

35 Glu Glu Ser Pro Phe Val Gly Asn Pro Gly Asn Ile Thr Gly Ala Arg

35 40 45

Gly Leu Thr Gly Thr Leu Arg Cys Gln Leu Gln Val Gln Gly Glu Pro

40 50 55 60

Pro Glu Val His Trp Leu Arg Asp Gly Gln Ile Leu Glu Leu Ala Asp

45 65 70 75 80

Ser Thr Gln Thr Gln Val Pro Leu Gly Glu Asp Glu Gln Asp Asp Trp

85 90 95

50 Ile Val Val Ser Gln Leu Arg Ile Thr Ser Leu Gln Leu Ser Asp Thr

100 105 110

55 Gly Gln Tyr Gln Cys Leu Val Phe Leu Gly His Gln Thr Phe Val Ser

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	Gln Ala Gln Gly Pro Pro Glu Pro Val Asp Leu Leu Trp Leu Gln Asp		
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	Ala Val Pro Leu Ala Thr Ala Pro Gly His Gly Pro Gln Arg Ser Leu		
20		180	185
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	His Val Pro Gly Leu Asn Lys Thr Ser Ser Phe Ser Cys Glu Ala His		
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25	Asn Ala Lys Gly Val Thr Thr Ser Arg Thr Ala Thr Ile Thr Val Leu		
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30	Pro Gln Gln Pro Arg Asn Leu His Leu Val Ser Arg Gln Pro Thr Glu		
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			240
	Leu Glu Val Ala Trp Thr Pro Gly Leu Ser Gly Ile Tyr Pro Leu Thr		
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			255
	His Cys Thr Leu Gln Ala Val Leu Ser Asp Asp Gly Met Gly Ile Gln		
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			270
	Ala Gly Glu Pro Asp Pro Pro Glu Glu Pro Leu Thr Ser Gln Ala Ser		
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			285
	Val Pro Pro His Gln Leu Arg Leu Gly Ser Leu His Pro His Pro Pro		
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55	Thr His Trp Leu Pro Val Glu Thr Pro Glu Gly Val Pro Leu Gly Pro		

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15	Leu Ala Tyr Gln Gly Gln Asp Thr Pro Glu Val Leu Met Asp Ile Gly		
	370	375	380
20	Leu Arg Gln Glu Val Thr Leu Glu Leu Gln Gly Asp Gly Ser Val Ser		
	385	390	395
25	Asn Leu Thr Val Cys Val Ala Ala Tyr Thr Ala Ala Gly Asp Gly Pro		
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30	Trp Ser Leu Pro Val Pro Leu Glu Ala Trp Arg Pro Gly Glu Ala Gln		
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35	Pro Val His Gln Leu Val Lys Glu Pro Ser Thr Pro Ala Phe Ser Trp		
	435	440	445
40	Pro Trp Trp Tyr Val Leu Leu Gly Ala Val Val Ala Ala Ala Cys Val		
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50	Tyr Gly Glu Val Phe Glu Pro Thr Val Glu Arg Gly Glu Leu Val Val		
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55	Arg Tyr Arg Val Arg Lys Ser Tyr Ser Arg Arg Thr Thr Glu Ala Thr		
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	Leu Asn Ser Leu Gly Ile Ser Glu Glu Leu Lys Glu Lys Leu Arg Asp		
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	Val Met Val Asp Arg His Lys Val Ala Leu Gly Lys Thr Leu Gly Glu		
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	Val	Thr	Met	Trp	Glu	Ile	Ala	Thr	Arg	Gly	Gln	Thr	Pro	Tyr	Pro	Gly
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Val Glu Asn Ser Glu Ile Tyr Asp Tyr Leu Arg Gln Gly Asn Arg Leu
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 Lys Gln Pro Ala Asp Cys Leu Asp Gly Leu Tyr Ala Leu Met Ser Arg
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 820 825 830
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 25 835 840 845
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	Leu Lys Glu Arg Trp Gly Ser Asn Glu Leu Pro Ala Glu Glu Gly Lys	
	35 40 45	
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	Thr Leu Leu Glu Leu Val Ile Glu Gln Phe Glu Asp Leu Leu Val Arg	
25	50 55 60	
	att tta tta ctg gca gca tgt ata tct ttt gtt ttg gct tgg ttt gaa	240
	Ile Leu Leu Leu Ala Ala Cys Ile Ser Phe Val Leu Ala Trp Phe Glu	
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	Leu Ile Leu Val Ala Asn Ala Ile Val Gly Val Trp Gln Glu Arg Asn	
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	Ala Glu Asn Ala Ile Glu Ala Leu Lys Glu Tyr Glu Pro Glu Met Gly	
	115 120 125	
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	Lys Val Tyr Arg Gln Asp Arg Lys Ser Val Gln Arg Ile Lys Ala Lys	
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 10 Pro Ala Asp Ile Arg Leu Thr Ser Ile Lys Ser Thr Thr Leu Arg Val
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 45 ttt ggg gaa cag ctt tcc aaa gtc atc tcc ctt att tgc att gca gtc 816
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	Val Ala Ala Ile Pro Glu Gly Leu Pro Ala Val Ile Thr Thr Cys Leu			
15	305	310	315	
	gct ctt gga act cgc aga atg gca aag aaa aat gcc att gtt cga agc	1008		
	Ala Leu Gly Thr Arg Arg Met Ala Lys Lys Asn Ala Ile Val Arg Ser			
20	320	325	330	335
	ctc ccg tct gtg gaa acc ctt ggt tgt act tct gtt atc tgc tca gac	1056		
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	340	345	350	
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20	Lys Ile Glu Arg Ala Asn Ala Cys Asn Ser Val Ile Lys Gln Leu Met			
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	Lys Lys Glu Phe Thr Leu Glu Phe Ser Arg Asp Arg Lys Ser Met Ser			
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35	ttt gtg aag ggt gct cct gaa ggt gtc att gac agg tgc acc cac att			1584
	Phe Val Lys Gly Ala Pro Glu Gly Val Ile Asp Arg Cys Thr His Ile			
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	cga gtt gga agt act aag gtt cct atg acc tct gga gtc aaa cag aag			1632
45	Arg Val Gly Ser Thr Lys Val Pro Met Thr Ser Gly Val Lys Gln Lys			
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50	alc atg tct gtc att cga gag tgg ggt agt ggc agc gac aca ctg cga			1680
	Ile Met Ser Val Ile Arg Glu Trp Gly Ser Gly Ser Asp Thr Leu Arg			
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 25 625 630 635
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 Ile Phe Gly Gln Asp Glu Asp Val Thr Ser Lys Ala Phe Thr Gly Arg
 30 640 645 650 655
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 Glu Phe Asp Glu Leu Asn Pro Ser Ala Gln Arg Asp Ala Cys Leu Asn
 35 660 665 670
 gcc cgc tgt ttt gct cga gtt gaa ccc tcc cac aag tct aaa atc gla 2064
 Ala Arg Cys Phe Ala Arg Val Glu Pro Ser His Lys Ser Lys Ile Val
 40 675 680 685
 gaa ttt ctt cag tct ttt gat gag att aca gct atg act ggc gat ggc 2112
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Val Asn Asp Ala Pro Ala Leu Lys Lys Ala Glu Ile Gly Ile Ala Met
5 705 710 715
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 740 745 750
20 atc tac aac aac atg aaa cag ttc atc cgc tac ctc atc tcg tcc aac 2304
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25 gtc ggg gaa gtt gtc tgt att ttc ctg aca gca gcc ctt gga ttt ccc 2352
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30 770 775 780
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45 atg aat aaa cct ccc cgg aac cca aag gaa cca ttg atc agc ggg tgg 2496
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 820 825 830
50 ctc ttt ttc cgt tac ttg gct att ggc tgt tac gtc ggc gct gct acc 2544
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5 glg ggl gct gct gca tgg tgg ttc att gct gct gac ggt ggt cca aga 2592
 Val Gly Ala Ala Ala Trp Trp Phe Ile Ala Ala Asp Gly Gly Pro Arg
 850 855 860

10 gtg tcc ttc tac cag ctg agt cat ttc cta cag tgt aaa gag gac aac 2640
 Val Ser Phe Tyr Gln Leu Ser His Phe Leu Gln Cys Lys Glu Asp Asn
 865 870 875

15 ccg gac ttt gaa ggc gtg gat tgt gca atc ttt gaa tcc cca tac ccg 2688
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 880 885 890 895

20 atg aca atg gcg ctc tct gtt cta gla act ata gaa atg tgt aac gcc 2736
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Glu Pro Ala Ile Leu Glu

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30

Lys Glu Arg Trp Gly Ser Asn Glu Leu Pro Ala Glu Glu Gly Lys Thr

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Arg Val Ala Leu Ser Val Leu Pro Gly Ser Arg Ala Leu Arg Pro Gly

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Lys Asp Arg Asp Val Thr Phe Ser Pro Ala Thr Ile Glu Asn Glu Leu

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Ile Lys Phe Cys Arg Glu Ala Arg Gly Lys Glu Asn Arg Leu Cys Tyr

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 Pro Gln Lys Arg Gly Arg Gly Arg Pro Arg Lys Gln Gln Gln Glu Pro

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35

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	Tyr	Phe	Lys	Cys
	Val			
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	Phe	Val	Ala	Ser
	Lys			
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	Leu	Cys	Ala	Thr
	Asp			
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	Val			
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	Asn	Leu	Arg	Ser
	Pro	Asn	Asn	Phe
	Leu			
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 5 His Leu Val His Ser Val Gln Arg Leu Phe Phe Thr Lys Ala Pro Ser
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 10 Leu Glu Gly Thr Ala Gly Lys Val Gly Gly Asn Gly Ser Lys Lys Gly
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 15 Gly Met Glu Asp Gly Lys Gly Arg Arg Ala Lys Ser Lys Glu Arg Ala
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 20 aag gct ggg gag ccc aaa cgg cgc agc cgc tcc aac atc tca ggc tgg 1047
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 30 Trp Ser Ser Asp Asp Asn Leu Asp Gly Glu Ala Gly Ala Phe Arg Ser
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 35 Ser Gly Pro Ala Ser Gly Leu Met Ile Leu Gly Arg Gln Ala Glu Arg
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 Ser Gln Pro Arg Tyr Phe Met His Ala Tyr Asn Thr Ile Ser Gly His
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 30 Arg Glu Thr Asp Ala Ala Ala Glu Gly Pro Ile Pro Cys Arg Arg Met
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 35 cgc agc ggc agc tac atc aag gcc atg ggc gac gag gac agc gac gag 1575
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 45 agc tat ctg agg gcc acg cag cag tgc ctg gga gag cag agc aac ccc 1671
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	Asn Asp Ser Ser Cys Ile Ser Gln Ile Phe Gly Gln Ala Ser Leu Ile			
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	Pro Gln Leu Phe Gly His Glu Gln Gln Val Arg Glu Ala Glu Leu Ser			
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30	aca gcg gca gag acg ctt gac ttg cca ctg ccc agc tac ttc cgc tcc	1959		
	Thr Ala Ala Glu Thr Leu Asp Leu Pro Leu Pro Ser Tyr Phe Arg Ser			
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	Arg Ser His Ser Tyr Leu Arg Ala Ile Gln Ala Gly Cys Ser Gln Glu			
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	Glu Asp Ser Val Ser Leu Gln Ser Leu Ser Pro Pro Pro Ser Thr Gly			
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	agc ctc agc aat agt cgc acg ctt ccg agt tca tca tgc cta glg gcg	2103		
	Ser Leu Ser Asn Ser Arg Thr Leu Pro Ser Ser Ser Cys Leu Val Ala			
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	tat aag aag acc ccg cca ccg gtc cct cca cgc acc act tca aag ccg	2151		
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	Phe Ile Ser Val Thr Val Gln Ser Ser Thr Glu Ser Ala Gln Asp Thr			
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	Tyr Leu Asp Ser Gln Asp His Lys Ser Glu Val Thr Ser Gln Ser Gly			
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	ctg agc aac tcg tcg gac agc ctg gac agc agt acc cga ccg ccc agc			2295
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	gtg aca cgg ggt gga gtc gcc cca gcc cct gag gcc cca gag cca ccc			2343
25	Val Thr Arg Gly Gly Val Ala Pro Ala Pro Glu Ala Pro Glu Pro Pro			
	625	630	635	
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	Pro Lys His Ala Ala Leu Lys Ser Glu Gln Gly Thr Leu Thr Ser Ser			
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	Glu Ser His Pro Glu Ala Ala Pro Lys Arg Lys Leu Ser Ser Ile Gly			
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55	ccc lct cac agt atg tcc tcc cga cgg gac aca gac tcg gat acc cag			2583

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	Pro Ser His Ser Met Ser Ser Arg Arg Asp Thr Asp Ser Asp Thr Gln	
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	Asp Ala Asn Asp Ser Ser Cys Lys Ser Ser Glu Arg Ser Leu Pro Asp	
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	tgt acc cct cac ccc aac tcc atc agc atc gat gcc ggt ccc cgg cag	2679
15	Cys Thr Pro His Pro Asn Ser Ile Ser Ile Asp Ala Gly Pro Arg Gln	
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25	agc gac cct gcc cta gag gcg tcc tcg ctg ccc cca ccc gac ccc tgg	2775
	Ser Asp Pro Ala Leu Glu Ala Ser Ser Leu Pro Pro Pro Asp Pro Trp	
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	Leu Glu Thr Ser Ser Ser Ser Pro Ala Glu Pro Ala Gln Pro Gly Ala	
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	Cys Arg Arg Asp Gly Tyr Trp Phe Leu Lys Leu Leu Gln Ala Glu Thr	
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	aac aac ctc tct gaa gaa gtc tta gga aaa gtc ctc agt gct gtg ggc	2967
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Leu

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Gln Asn Thr Leu Pro Gly Asp Gly Leu Phe Pro Leu Asn Asn Gln Leu

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Pro Pro Pro Ser Ser Thr Phe Pro Arg Ile His Tyr Asn Ser His Phe

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65 70 75 80

Glu Val Pro Glu Glu Ser Pro Phe Pro Ser His Ala Gln Ala Thr Lys

85 90 95

40

Ile Asn Arg Leu Pro Ala Asn Leu Leu Asp Gln Phe Glu Lys Gln Leu

100 105 110

45

Pro Ile His Arg Asp Gly Phe Ser Thr Leu Gln Phe Pro Arg Gly Glu

115 120 125

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Ser Val Gln Arg Leu Phe Phe Thr Lys Ala Pro Ser Leu Glu Gly Thr

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	Pro Lys Arg Arg Ser Arg Ser Asn Ile Ser Gly Trp Trp Ser Ser Asp		
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	Thr Lys Asn Asn Thr Thr Glu Leu Thr Ala Pro Pro Pro Pro Pro Ala		
30		260	265 270
	Pro Pro Ala Thr Cys Pro Ser Leu Gly Val Gly Thr Asp Thr Asn Tyr		
		275	280 285
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	Val Lys Arg Gly Ser Trp Ser Thr Leu Thr Leu Ser His Ala His Glu		
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	Val Cys Gln Lys Thr Ser Ala Thr Leu Asp Lys Ser Leu Leu Lys Ser		
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	Lys Ser Cys His Gln Gly Leu Ala Tyr His Tyr Leu Gln Val Pro Gly		
		325	330 335
	Gly Gly Gly Glu Trp Ser Thr Thr Leu Leu Ser Pro Arg Glu Thr Asp		
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	Ala Ala Ala Glu Gly Pro Ile Pro Cys Arg Arg Met Arg Ser Gly Ser		
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Tyr Ile Lys Ala Met Gly Asp Glu Asp Ser Asp Glu Ser Gly Gly Ser
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 Pro Lys Pro Ser Pro Lys Thr Ala Ala Arg Arg Gln Ser Tyr Leu Arg
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 420 425 430
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	Glu Ala Ala Pro Lys Arg Lys Leu Ser Ser Ile Gly Ile Gln Glu Arg		
25		660	665
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	Thr Arg Arg Asn Gly Ser His Leu Ser Glu Asp Asn Gly Pro Lys Ala		
	675	680	685
30	Ile Asp Val Met Ala Pro Ser Ser Glu Ser Ser Val Pro Ser His Ser		
	690	695	700
35	Met Ser Ser Arg Arg Asp Thr Asp Ser Asp Thr Gln Asp Ala Asn Asp		
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	Ser Ser Cys Lys Ser Ser Glu Arg Ser Leu Pro Asp Cys Thr Pro His		
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	Pro Asn Ser Ile Ser Ile Asp Ala Gly Pro Arg Gln Ala Pro Lys Ile		
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			750
	Ala Gln Ile Lys Arg Asn Leu Ser Tyr Gly Asp Asn Ser Asp Pro Ala		
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	805	810	815	
10	Gly Trp Cys Cys Gln Met Asp Lys	Glu Thr Lys Glu Asn Asn Leu Ser		
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20	Leu Met Ser Gln Lys Phe Gln Gln Phe Arg	Gly Leu Cys Glu Gln Asn		
	850	855	860	
25	Leu Asn Pro Asp Ala Asn Pro Arg Pro Thr Ala	Gln Asp Leu Ala Gly		
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30	Phe Trp Asp Leu Leu Gln Leu Ser Ile Glu Asp	Ile Ser Met Lys Phe		
	885	890	895	
35	Asp Glu Leu Tyr His Leu Lys Ala Asn Ser Trp	Gln Leu Val Glu Thr		
	900	905	910	
40	Pro Glu Lys Arg Lys Glu Glu Lys Lys Pro Pro	Pro Pro Val Pro Lys		
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45	Lys Pro Ala Lys Ser Lys Pro Ala Val Ser Arg	Asp Lys Ala Ser Asp		
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55	Lys Arg Ala Ala Ser Val Arg Gln Asn Ser Ala	Thr Glu Ser Ala Asp		
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Arg Gly Gln Val Ala Lys Leu Glu Ala Ala Leu Gly Glu Ala Lys Lys

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Gln Leu Gln Asp Glu Met Leu Arg Arg Val Asp Ala Glu Asn Arg Leu

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	Gln Lys Gln Leu Ala Ala Lys Glu Ala Lys Leu Arg Asp Leu Glu Asp		
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	Ser Leu Ala Arg Glu Arg Asp Thr Ser Arg Arg Leu Leu Ala Glu Lys		
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	Glu Arg Glu Met Ala Glu Met Arg Ala Arg Met Gln Gln Gln Leu Asp		
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	Ser Pro Ser Pro Thr Ser Gln Arg Ser Arg Gly Arg Ala Ser Ser His		
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	Asn Val Asn Thr Arg Cys Gln Lys Ile Cys Asp Gln Trp Asp Ala Leu				
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45	Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp Arg Glu Arg				
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15	Ile Phe Asp Asn Lys His Thr Asn Tyr Thr Met Glu His Ile Arg Val					
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20	Gly Trp Glu Gln Leu Leu Thr Thr Ile Ala Arg Thr Ile Asn Glu Val					
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25	Glu Asn Gln Ile Leu Thr Arg Asp Ala Lys Gly Ile Ser Gln Glu Gln					
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	Met Gln Glu Phe Arg Ala Ser Phe Asn His Phe Asp Lys Asp His Gly					
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	Gly Ala Leu Gly Arg Gly Val Gln Gly Leu Pro His Gln Pro Gly Leu					
	785		790		795	800
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		805		810		815
40	Ser Leu Val Asp Pro Asn His Ser Gly Leu Val Thr Phe Gln Ala Phe					
		820		825		830
45	Ile Asp Phe Met Ser Arg Glu Thr Thr Asp Thr Asp Thr Ala Asp Gln					
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	Val Ile Thr Ser Phe Lys Val Leu Ala Gly Asp Lys Asn Phe Ile Thr					
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55		865		870		875
						880

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895

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Met Pro Ser

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Thr Glu Lys Asp Leu Ala Glu Asp Ala Pro Trp Lys Lys Ile Gln Gln

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Asn Thr Phe Thr Arg Trp Cys Asn Glu His Leu Lys Cys Val Gly Lys

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25

30

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cgc ctg acc gac ctg cag cgc gac ctc agc gac ggg ctc cgg ctc atc 262

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Arg Leu Thr Asp Leu Gln Arg Asp Leu Ser Asp Gly Leu Arg Leu Ile

40

45

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gcg ctg ctc gag glg ctc agc cag aag cgc atg tac cgc aag ttc cal 310

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	Pro Arg Pro Asn Phe Arg Gln Met Lys Leu Glu Asn Val Ser Val Ala	
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20	Lys Ala Ile Val Asp Gly Asn Leu Lys Leu Ile Leu Gly Leu Ile Trp	
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	Thr Leu Ile Leu His Tyr Ser Ile Ser Met Pro Met Trp Glu Asp Glu	
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	Pro Gly Leu Cys Pro Asp Trp Glu Ala Trp Asp Pro Asn Gln Pro Val	
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 Gly Asp Val Ala Val Val Ile Val Asp Pro Gln Gly Arg Arg Asp Thr
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	630	635	640	
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	Thr Gly Cys Ile Val Asp Lys Pro Ala Glu Phe Thr Ile Asp Ala Arg			
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	Cys Pro Ile Asp Ile Lys Val Ile Pro Asn Gly Asn Gly Thr Phe Arg			
	695	700	705	
35	tgc tcc tac gtg ccc acc aag ccc att aag cac acc atc atc atc tcc			2278
	Cys Ser Tyr Val Pro Thr Lys Pro Ile Lys His Thr Ile Ile Ile Ser			
	710	715	720	
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	805	810	815	
25	cgc tac acc atc atg gtg ctg ttt gcc aac cag gag atc ccc gcc agc			2614
	Arg Tyr Thr Ile Met Val Leu Phe Ala Asn Gln Glu Ile Pro Ala Ser			
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	Pro Phe His Ile Lys Val Asp Pro Ser His Asp Ala Ser Lys Val Lys			
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	870	875	880	
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 20 Lys Ile Lys Val Gln Gly Leu Asn Ser Lys Val Ala Val Gly Gln Glu
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 25 caa gca ttc tct gtg aac aca cga ggg gct ggc ggt cag ggc caa ctg 3046
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 20 acc cgt gtc cat gtg cag cct gcc gtc gat acc agt ggc gtc aag gtc 3814
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 1240 1245 1250
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 Ser Gly Pro Gly Val Glu Pro His Gly Val Leu Arg Glu Val Thr Thr
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	Gln Pro Tyr Ala Pro Pro Arg Pro Gly Ala Arg Pro Thr His Trp Ala			
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20	Asp Asn Lys Asp Gly Thr Ile Thr Val Arg Tyr Ala Pro Thr Glu Lys	
	1800 1805 1810	
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	1815 1820 1825	
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35	1830 1835 1840	
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40	Ala Tyr Gly Pro Gly Leu Ser His Gly Met Val Asn Lys Pro Ala Thr	
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45	Phe Thr Ile Val Thr Lys Asp Ala Gly Glu Gly Gly Leu Ser Leu Ala	
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50	Val Glu Gly Pro Ser Lys Ala Glu Ile Thr Cys Lys Asp Asn Lys Asp	
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Gly Thr Cys Thr Val Ser Tyr Leu Pro Thr Ala Pro Gly Asp Tyr Ser
 5 1895 1900 1905
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 10 Ile Ile Val Arg Phe Asp Asp Lys His Ile Pro Gly Ser Pro Phe Thr
 1910 1915 1920
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 15 Ala Lys Ile Thr Gly Asp Asp Ser Met Arg Thr Ser Gln Leu Asn Val
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 Asp Ala Ser Lys Val Arg Val Trp Gly Lys Gly Leu Ser Glu Gly His
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 15 Cys Glu Asp Met Glu Asp Gly Thr Cys Lys Val Thr Tyr Cys Pro Thr
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 20 gag ccc ggc acc tac atc atc aac atc aag ttt gct gac aag cac gtg 6406
 20 Glu Pro Gly Thr Tyr Ile Ile Asn Ile Lys Phe Ala Asp Lys His Val
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	Ala Arg Arg Leu Thr Val Thr Ser Leu Gln Glu Thr Gly Leu Lys Val			
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	Pro Gly Ser Pro Phe Lys Ile Arg Val Gly Glu Gln Ser Gln Ala Gly			
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	acc ggt gtg tca tca gag ttc atc gtg aac acc ctg aat gcc ggc tgc			7654
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	Gly Ala Leu Ser Val Thr Ile Asp Gly Pro Ser Lys Val Gln Leu Asp			
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	Gly His Ser Leu His Glu Thr Ser Thr Val Leu Val Glu Thr Val Thr			
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 20 Gly Thr Asn Met Met Met Val Gly Val His Gly Pro Lys Thr Pro Cys
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 25 gag gag gtg tac gtg aag cac atg ggg aac cgg gtg tac aat gtc acc 8134
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 30 tac act gtc aag gag aaa ggg gac tac atc ctc att gtc aag tgg ggt 8182
 Tyr Thr Val Lys Glu Lys Gly Asp Tyr Ile Leu Ile Val Lys Trp Gly
 35 2680 2685 2690
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<211> 2705

<212> PRT

<213> Homo sapiens

<400> 44

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Val Gly Lys Arg Leu Thr Asp Leu Gln Arg Asp Leu Ser Asp Gly Leu

35 40 45

Arg Leu Ile Ala Leu Leu Glu Val Leu Ser Gln Lys Arg Met Tyr Arg

50 55 60

Lys Phe His Pro Arg Pro Asn Phe Arg Gln Met Lys Leu Glu Asn Val

65 70 75 80

Ser Val Ala Leu Glu Phe Leu Glu Arg Glu His Ile Lys Leu Val Ser

85 90 95

Ile Asp Ser Lys Ala Ile Val Asp Gly Asn Leu Lys Leu Ile Leu Gly

100 105 110

Leu Ile Trp Thr Leu Ile Leu His Tyr Ser Ile Ser Met Pro Met Trp

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10	Leu Leu Gly Trp Ile Gln Asn Lys Val Pro Gln Leu Pro Ile Thr Asn			
	145	150	155	160
	Phe Asn Arg Asp Trp Gln Asp Gly Lys Ala Leu Gly Ala Leu Val Asp			
15	165	170	175	
	Asn Cys Ala Pro Gly Leu Cys Pro Asp Trp Glu Ala Trp Asp Pro Asn			
20	180	185	190	
	Gln Pro Val Glu Asn Ser Arg Glu Ala Met Gln Gln Ala Asp Asp Trp			
	195	200	205	
25	Leu Gly Val Pro Gln Val Ile Ala Pro Glu Glu Ile Val Asp Pro Asn			
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30	Val Asp Glu His Ser Val Met Thr Tyr Leu Ser Gln Phe Pro Lys Ala			
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	Lys Leu Lys Pro Gly Ala Pro Val Arg Ser Lys Gln Leu Asn Pro Lys			
35	245	250	255	
	Lys Ala Ile Ala Tyr Gly Pro Gly Ile Glu Pro Gln Gly Asn Thr Val			
40	260	265	270	
	Leu Gln Pro Ala His Phe Thr Val Gln Thr Val Asp Ala Gly Val Gly			
45	275	280	285	
	Glu Val Leu Val Tyr Ile Glu Asp Pro Glu Gly His Thr Glu Glu Ala			
	290	295	300	
50	Lys Val Val Pro Asn Asn Asp Lys Asp Arg Thr Tyr Ala Val Ser Tyr			
	305	310	315	320
55	Val Pro Lys Val Ala Gly Leu His Lys Val Thr Val Leu Phe Ala Gly			

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5	Gln Asn Ile Glu Arg Ser Pro Phe Glu Val Asn Val Gly Met Ala Leu		
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10	Gly Asp Ala Asn Lys Val Ser Ala Arg Gly Pro Gly Leu Glu Pro Val		
	355	360	365
15	Gly Asn Val Ala Asn Lys Pro Thr Tyr Phe Asp Ile Tyr Thr Ala Gly		
	370	375	380
20	Ala Gly Thr Gly Asp Val Ala Val Val Ile Val Asp Pro Gln Gly Arg		
	385	390	395
	Arg Asp Thr Val Glu Val Ala Leu Glu Asp Lys Gly Asp Ser Thr Phe		
	405	410	415
25	Arg Cys Thr Tyr Arg Pro Ala Met Glu Gly Pro His Thr Val His Val		
	420	425	430
30	Ala Phe Ala Gly Ala Pro Ile Thr Arg Ser Pro Phe Pro Val His Val		
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35	Ser Glu Ala Cys Asn Pro Asn Ala Cys Arg Ala Ser Gly Arg Gly Leu		
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40	Gln Pro Lys Gly Val Arg Val Lys Glu Val Ala Asp Phe Lys Val Phe		
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	Thr Lys Gly Ala Gly Ser Gly Glu Leu Lys Val Thr Val Lys Gly Pro		
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45	Lys Gly Thr Glu Glu Pro Val Lys Val Arg Glu Ala Gly Asp Gly Val		
	500	505	510
50	Phe Glu Cys Glu Tyr Tyr Pro Val Val Pro Gly Lys Tyr Val Val Thr		
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55	Ile Thr Trp Gly Gly Tyr Ala Ile Pro Arg Ser Pro Phe Glu Val Gln		
	530	535	540

Val Ser Pro Glu Ala Gly Val Gln Lys Val Arg Ala Trp Gly Pro Gly
 5 545 550 555 560
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 10 565 570 575
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 15 Gln Ala Lys Ile Glu Cys Asp Asp Lys Gly Asp Gly Ser Cys Asp Val
 595 600 605
 20 Arg Tyr Trp Pro Thr Glu Pro Gly Glu Tyr Ala Val His Val Ile Cys
 610 615 620
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 25 625 630 635 640
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 30 645 650 655
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	Cys Ala Pro Gly Val Val Gly Pro Ala Glu Ala Asp Ile Asp Phe Asp
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	820 825 830
	Pro Ala Ser Pro Phe His Ile Lys Val Asp Pro Ser His Asp Ala Ser
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	Thr Ala Val Gln Gln Gly Asn Met Ala Val Thr Val Thr Tyr Gly Gly
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	Asp Pro Val Pro Lys Ser Pro Phe Val Val Asn Val Ala Pro Pro Leu
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	Asp Leu Ser Lys Ile Lys Val Gln Gly Leu Asn Ser Lys Val Ala Val
	945 950 955 960
55	Glv Gln Glu Gln Ala Phe Ser Val Asn Thr Arg Gly Ala Gly Gly Gln

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	995	1000	1005
15	Met Pro Pro Glu Glu Gly Pro Tyr Lys Val Asp Ile Thr Tyr Asp Gly		
	1010	1015	1020
	His Pro Val Pro Gly Ser Pro Phe Ala Val Glu Gly Val Leu Pro Pro		
20	1025	1030	1035
	Asp Pro Ser Lys Val Cys Ala Tyr Gly Pro Gly Leu Lys Gly Gly Leu		
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25	Val Gly Thr Pro Ala Pro Phe Ser Ile Asp Thr Lys Gly Ala Gly Thr		
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30	Gly Gly Leu Gly Leu Thr Val Glu Gly Pro Cys Glu Ala Lys Ile Glu		
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	Cys Gln Asp Asn Gly Asp Gly Ser Cys Ala Val Ser Tyr Leu Pro Thr		
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	Glu Pro Gly Glu Tyr Thr Ile Asn Ile Leu Phe Ala Glu Ala His Ile		
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	Pro Gly Ser Pro Phe Lys Ala Thr Ile Arg Pro Val Phe Asp Pro Ser		
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45	Lys Val Arg Ala Ser Gly Pro Gly Leu Glu Arg Gly Lys Val Gly Glu		
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50	Ala Ala Thr Phe Thr Val Asp Cys Ser Glu Ala Gly Glu Ala Glu Leu		
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	Val Lys Val Ser Gly Pro Gly Val Glu Pro His Gly Val Leu Arg Glu			
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	1540 1545 1550
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	1555 1560 1565
	Asn Ile Arg Asp Asn Gly Asp Gly Thr Tyr Ala Val Ser Tyr Leu Pro
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	Asp Met Ser Gly Arg Tyr Thr Ile Thr Ile Lys Tyr Gly Gly Asp Glu
55	1585 1590 1595 1600

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25						1665					1670					1675
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5	Ile	Pro	Gly	Ser
	Pro	Leu	Gln	Phe
	Tyr	Val	Asp	Ala
	Ile	Asn	Ser	Arg
	1825	1830	1835	1840
10	His	Val	Ser	Ala
	Tyr	Gly	Pro	Gly
	Leu	Ser	His	Gly
	Met	Val	Asn	Lys
	1845	1850	1855	
15	Pro	Ala	Thr	Phe
	Thr	Ile	Val	Thr
	Lys	Asp	Ala	Gly
	Glu	Gly	Gly	Leu
	1860	1865	1870	
20	Ser	Leu	Ala	Val
	Glu	Gly	Pro	Ser
	Lys	Ala	Glu	Ile
	Thr	Cys	Lys	Asp
	1875	1880	1885	
25	Asn	Lys	Asp	Gly
	Thr	Cys	Thr	Val
	Ser	Tyr	Leu	Pro
	Thr	Ala	Pro	Gly
	1890	1895	1900	
30	Asp	Tyr	-Ser	Ile
	Ile	Val	Arg	Phe
	Asp	Asp	Lys	His
	Ile	Pro	Gly	Ser
	1905	1910	1915	1920
35	Pro	Phe	Thr	Ala
	Lys	Ile	Thr	Gly
	Asp	Asp	Ser	Met
	Arg	Thr	Ser	Gln
	1925	1930	1935	
40	Leu	Asn	Val	Gly
	Thr	Ser	Thr	Asp
	Val	Ser	Leu	Lys
	Ile	Thr	Glu	Ser
	1940	1945	1950	
45	Asp	Leu	Ser	Gln
	Leu	Thr	Ala	Ser
	Ile	Arg	Ala	Pro
	Ser	Gly	Asn	Glu
	1955	1960	1965	
50	Glu	Pro	Cys	Leu
	Leu	Lys	Arg	Leu
	Pro	Asn	Arg	His
	Ile	Gly	Ile	Ser
	1970	1975	1980	
55	Phe	Thr	Pro	Lys
	Glu	Val	Gly	Glu
	His	Val	Val	Ser
	Val	Arg	Lys	Ser
	1985	1990	1995	2000
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	Thr	Asn	Ser	Pro
	Phe	Lys	Ile	Leu
	Val	Gly	Pro	Ser
	2005	2010	2015	
65	Glu	Ile	Gly	Asp
	Ala	Ser	Lys	Val
	Arg	Val	Trp	Gly
	Lys	Gly	Leu	Ser

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10	Ala Gly Tyr Gly Gly Leu Gly Leu Ser Ile Glu Gly Pro Ser Lys Val		
	2050	2055	2060
	Asp Ile Asn Cys Glu Asp Met Glu Asp Gly Thr Cys Lys Val Thr Tyr		
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	Cys Pro Thr Glu Pro Gly Thr Tyr Ile Ile Asn Ile Lys Phe Ala Asp		
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25	Arg Met Lys Glu Ser Ile Thr Arg Arg Arg Gln Ala Pro Ser Ile Ala		
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	Arg Gly Gly Glu Thr Lys Pro Glu Val Arg Val Glu Glu Ser Thr Gln		
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45	Val Gly Gly Asp Pro Phe Pro Ala Val Phe Gly Asp Phe Leu Gly Arg		
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50	Glu Arg Leu Gly Ser Phe Gly Ser Ile Thr Arg Gln Gln Glu Gly Glu		
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	Ala Ser Ser Gln Asp Met Thr Ala Gln Val Thr Ser Pro Ser Gly Lys		
55	2225	2230	2235 2240

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	Arg	Phe	Val	Pro	Gln	Glu	Met	Gly	Pro	His	Thr	Val	Ala	Val	Lys	Tyr
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	Arg	Gly	Gln	His	Val	Pro	Gly	Ser	Pro	Phe	Gln	Phe	Thr	Val	Gly	Pro
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	Leu	Gly	Glu	Gly	Gly	Ala	His	Lys	Val	Arg	Ala	Gly	Arg	Ala	Gly	Leu
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	Glu	Arg	Gly	Val	Ala	Gly	Val	Pro	Ala	Glu	Phe	Ser	Ile	Trp	Thr	Arg
25					2305					2310						2320
	Glu	Ala	Gly	Ala	Gly	Gly	Leu	Ser	Ile	Ala	Val	Glu	Gly	Pro	Ser	Lys
30					2325					2330						2335
	Ala	Glu	Ile	Ala	Phe	Glu	Asp	Arg	Lys	Asp	Gly	Ser	Cys	Gly	Val	Ser
35					2340					2345						2350
	Tyr	Val	Val	Gln	Glu	Pro	Gly	Asp	Tyr	Glu	Val	Ser	Ile	Lys	Phe	Asn
40					2355					2360						2365
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	Ser	Asp	Asp	Ala	Arg	Arg	Leu	Thr	Val	Thr	Ser	Leu	Gln	Glu	Thr	Gly
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60					2420					2425						2430
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65					2435					2440						2445

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 10 Gln Ala Gly Asp Pro Gly Leu Val Ser Ala Tyr Gly Pro Gly Leu Glu
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 Pro Met Ala Pro Gly Asn Tyr Leu Ile Ala Ile Lys Tyr Gly Gly Pro
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 Gln His Ile Val Gly Ser Pro Phe Lys Ala Lys Val Thr Gly Pro Arg
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 35 Leu Ser Gly Gly His Ser Leu His Glu Thr Ser Thr Val Leu Val Glu
 2580 2585 2590
 Thr Val Thr Lys Ser Ser Ser Ser Arg Gly Ser Ser Tyr Ser Ser Ile
 40 2595 2600 2605
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 50 2625 2630 2635 2640
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2660 2665 2670
 5 Asn Val Thr Tyr Thr Val Lys Glu Lys Gly Asp Tyr Ile Leu Ile Val
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15	Ala Lys Gln Leu Asn Glu Asp Cys Ser Lys Thr Gln Pro Cys Asp His				
		60	65	70	
	acc aag ggg ctg gaa tgc aac ttc ggc gcc agc tcc acc gct ctg aag				473
20	Thr Lys Gly Leu Glu Cys Asn Phe Gly Ala Ser Ser Thr Ala Leu Lys				
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	Gly Ile Cys Arg Ala Gln Ser Glu Gly Arg Pro Cys Glu Tyr Asn Ser				
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30	aga atc tac caa aac ggg gaa agt ttc cag ccc aac tgt aaa cat cag				569
	Arg Ile Tyr Gln Asn Gly Glu Ser Phe Gln Pro Asn Cys Lys His Gln				
35	105	110	115	120	
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	Cys Thr Cys Ile Asp Gly Ala Val Gly Cys Ile Pro Leu Cys Pro Gln				
40		125	130	135	
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45	Glu Leu Ser Leu Pro Asn Leu Gly Cys Pro Asn Pro Arg Leu Val Lys				
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35 40 45

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50 ~ 55 60

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Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val

115 120 125

Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly

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25	Arg Gln Pro Pro Tyr Ser Pro His His Ser Pro Thr Pro Ser Pro His			
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 15 Ser Ser Asn Val Ser Pro Ala Leu Pro Leu Pro Thr Ala His Ser Thr
 50 55 60
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 20 65 70 75 80
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 30 Pro Ala Leu Glu Ser Pro Arg Ile Glu Ile Thr Ser Cys Leu Gly Leu
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 35 Tyr His Asn Asn Asn Gln Phe Phe His Asp Val Glu Val Glu Asp Val
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	Arg Gln Pro Pro Tyr	Ser Pro His His	Ser Pro Thr Pro	Ser Pro His
20	275	280	285	
	Gly Ser Pro Arg Val	Ser Val Thr Asp Asp	Ser Trp Leu Gly	Asn Thr
	290	295	300	
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	305	310	315	320
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	Lys Thr Thr Leu Glu	Gln Pro Pro Ser	Val Ala Leu Lys	Val Glu Pro
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	Val Gly Glu Asp Leu	Gly Ser Pro Pro	Pro Pro Ala Asp	Phe Ala Pro
40	355	360	365	
	Glu Asp Tyr Ser Ser	Phe Gln His Ile	Arg Lys Gly Gly	Phe Cys Asp
	370	375	380	
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	385	390	395	400
50	Pro Leu Ser Pro Thr	Ser Tyr Met Ser	Pro Thr Leu Pro	Ala Leu Asp
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 660 665 670
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	His Gly His Ala Gly His His His His His His His His His His His	
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25	ccg ccc atg atc gct ctg cag ccg ctg gtc acc gag gag ccg acc cag	528
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	Val His His His Gln Glu Val Ile Leu Val Gln Thr Arg Glu Glu Val	
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	gat cag att ctg atc ccg gtg ccc gcc ccg gcc ggc ggc gag gag gag	672
45	Asp Gln Ile Leu Ile Pro Val Pro Ala Pro Ala Gly Gly Asp Asp Asp	
	130 135 140	
50	tac att gaa caa acg ctg gtc acc gtg gcg gcg gcc ggc aag agc ggc	720
	Tyr Ile Glu Gln Thr Leu Val Thr Val Ala Ala Ala Gly Lys Ser Gly	
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 55 Pro Pro Met Ile Ala Leu Gln Pro Leu Val Thr Asp Asp Pro Thr Gln
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	Val His His His Gln Glu Val Ile Leu Val Gln Thr Arg Glu Glu Val
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	Gly Lys Lys Leu Pro Pro Gly Gly Ile Pro Gly Ile Asp Leu Ser Asp
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	Pro Lys Gln Leu Ala Glu Phe Ala Arg Met Lys Pro Arg Lys Ile Lys
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Lys Met Phe Arg Asp Asn Ser Ala Met Arg Lys His Leu His Thr His
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268

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 5 135 140 145
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25 Val Thr Thr Val Asp Met Thr Arg Lys Pro Glu Glu Leu Lys Asp Leu

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Ala Pro Gly Thr Asn Pro Pro Phe Leu Val Tyr Asn Lys Glu Leu Lys

30 65 70 75 80

Thr Asp Phe Ile Lys Ile Glu Glu Phe Leu Glu Gln Thr Leu Ala Pro

85 90 95

35 Pro Arg Tyr Pro His Leu Ser Pro Lys Tyr Lys Glu Ser Phe Asp Val

100 105 110

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 Glu Val Val Gly Arg Leu Ile Leu Gly Ala His Ser Val Thr Ala Ser
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	Ala Glu Ser Gln Ile Leu Lys His Leu Leu Lys Asn Leu Phe Lys Ile				
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	Trp Leu Lys Lys Glu Pro Glu Ala Phe Asp Trp Ser Pro Val Val Thr				
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	tat gtg tgt gat ctt gaa ggg aac aga gtc aag ggt cca gag aag gag	501			
	Tyr Val Cys Asp Leu Glu Gly Asn Arg Val Lys Gly Pro Glu Lys Glu				
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 25 cag aag ttc tcc agc ctc ccc ctg gcc cgg gag gca gta gag gct gct 789
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<213> Homo sapiens

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Pro Arg Asp Tyr Leu Glu Lys Tyr Tyr Lys Phe Gly Ser Arg His Ser

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Ala Glu Ser Gln Ile Leu Lys His Leu Leu Lys Asn Leu Phe Lys Ile

35 40 45

20

Phe Cys Leu Asp Gly Val Lys Gly Asp Leu Leu Ile Asp Ile Gly Ser

50 55 60

25

Gly Pro Thr Ile Tyr Gln Leu Leu Ser Ala Cys Glu Ser Phe Lys Glu

65 70 75 80

Ile Val Val Thr Asp Tyr Ser Asp Gln Asn Leu Gln Glu Leu Glu Lys

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Trp Leu Lys Lys Glu Pro Glu Ala Phe Asp Trp Ser Pro Val Val Thr

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35

Tyr Val Cys Asp Leu Glu Gly Asn Arg Val Lys Gly Pro Glu Lys Glu

115 120 125

40

Glu Lys Leu Arg Gln Ala Val Lys Gln Val Leu Lys Cys Asp Val Thr

130 135 140

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Gln Ser Gln Pro Leu Gly Ala Val Pro Leu Pro Pro Ala Asp Cys Val

145 150 155 160

Leu Ser Thr Leu Cys Leu Asp Ala Ala Cys Pro Asp Leu Pro Thr Tyr

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Cys Arg Ala Leu Arg Asn Leu Gly Ser Leu Leu Lys Pro Gly Gly Phe

55

180 185 190

EP 1 225 224 A1

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 5 Gln Lys Phe Ser Ser Leu Pro Leu Gly Arg Glu Ala Val Glu Ala Ala
 210 215 220
 10 Val Lys Glu Ala Gly Tyr Thr Ile Glu Trp Phe Glu Val Ile Ser Gln
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 25 tgg gga gtt tgt tgg gtg aac ttt gag gcg ctg atc atc acc atg tgc 402
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 40 120 125 130 135
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 35 40 45
 45 Glu Glu Cys Leu Lys Asn Val Ser Cys Leu Trp Cys Asn Thr Asn Lys
 50 55 60
 Ala Cys Leu Asp Tyr Pro Val Thr Ser Val Leu Pro Pro Ala Ser Leu
 50 65 70 75 80
 Cys Lys Leu Ser Ser Ala Arg Trp Gly Val Cys Trp Val Asn Phe Glu
 55 85 90 95

Ala Leu Ile Ile Thr Met Ser Val Val Gly Gly Thr Leu Leu Leu Gly
 100 105 110
 5 Ile Ala Ile Cys Cys Cys Cys Cys Arg Arg Lys Arg Ser Arg Lys
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 10 Pro Asp Arg Ser Glu Glu Lys Ala Met Arg Glu Arg Glu Glu Arg Arg
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 ccg gga aca cct gat ttt cat aca atc cca gca ttt tgt ttg act cca 717
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	Thr Ala Asp Ala Gln Leu Cys Asn His Gln Thr Cys Pro Met Lys Ala			
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25	cta aat gtt gag gct gca aga aag aac ala cca tgt gcc gct gtg tca	1053		
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	Pro Asn Arg Ser Lys Cys Glu Arg Asn Thr Val Ala Asp Val Asp Glu			
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25 <211> 469

<212> PRT

30 <213> Homo sapiens

<400> 60

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 10 Ser Pro Val Ser Ala Pro Lys Leu Pro Lys Ala Gln Ala Thr Ser Val
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 15 Ile Arg His Thr Ala Asp Ala Gln Leu Cys Asn His Gln Thr Cys Pro
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 20 Met Lys Ala Ala Ser Ile Leu Asn Tyr Gln Asn Asn Ser Phe Arg Arg
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 25 180 185 190
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 40 Gln Lys Ser Val Leu Val Ser Pro Pro Ala Val Ser Ala Gly Gly Val
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 30 Lys Phe Ala Cys Pro Met Cys Asp Arg Arg Phe Met Arg Ser Asp His
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 Cys Arg Ile Tyr Val Gly Asn Leu Pro Pro Asp Ile Arg Thr Lys Asp
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 25 gat aac act aag ttt aga tct cat gag gga gaa act gcc tac atc cgg 697
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Asn Arg Arg Gly Gly Pro Pro Phe Ala Phe Val Glu Phe Glu Asp Pro

50 50 55 60

Arg Asp Ala Glu Asp Ala Val Tyr Gly Arg Asp Gly Tyr Asp Tyr Asp

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Gly Tyr Arg Leu Arg Val Glu Phe Pro Arg Ser Gly Arg Gly Thr Gly

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 Gly Pro Pro Ser Arg Arg Ser Glu Asn Arg Val Val Val Ser Gly Leu
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 Pro Pro Ser Gly Ser Trp Gln Asp Leu Lys Asp His Met Arg Glu Ala
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 20 Glu Phe Val Arg Lys Glu Asp Met Thr Tyr Ala Val Arg Lys Leu Asp
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 Ser Arg Ser Arg Ser Arg Ser Arg Ser Arg Ser Asn Ser Arg Ser Arg
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Met Asp Leu Leu Pro Pro Lys Pro Lys Tyr Asn Pro

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ctc cgg aat gag tct ctg tca tgc ctg gag gaa ggg gct tct ggg tcc 278

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Leu Arg Asn Glu Ser Leu Ser Ser Leu Glu Glu Gly Ala Ser Gly Ser

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acc ccc ccg gag gag ctg cct tcc cca tca gct tca tcc ctg ggg ccc 326

Thr Pro Pro Glu Glu Leu Pro Ser Pro Ser Ala Ser Ser Leu Gly Pro

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atc ctg cct cct ctg cct ggg gac gat agt ccc act acc ctg tgc tcc 374

Ile Leu Pro Pro Leu Pro Gly Asp Asp Ser Pro Thr Thr Leu Cys Ser

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Phe Phe Pro Arg Met Ser Asn Leu Arg Leu Ala Asn Pro Ala Gly Gly

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Arg Pro Gly Ser Lys Gly Glu Pro Gly Arg Ala Ala Asp Asp Gly Glu

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Gly Ile Asp Gly Ala Ala Met Pro Glu Ser Gly Pro Leu Pro Leu Leu

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95

100

105

EP 1 225 224 A1

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	ccc ccc aat cct gct atc aat ggc agt gca ccc cgg gac ctg ttt gac	1574		
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30	atg aag ccc ttc gaa gat gct ctt cgg gtg cct cca cct ccc cag tgc	1622		
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35	gtg tcc atg gct gag cag ctc cga ggg gag ccc tgg ttc cat ggg aag	1670		
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	ctg agc cgg cgg gag gct gag gca ctg ctg cag ctc aal ggg gac ttc	1718		
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	tig gta cgg gag agc acg acc aca cct ggc cag tat gtg ctc act ggc	1766		
	Leu Val Arg Glu Ser Thr Thr Thr Pro Gly Gln Tyr Val Leu Thr Gly			
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	tig cag agt ggg cag cct aag cat ttg cta ctg gtg gac cct gag ggt	1814		
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 Ser Tyr His Met Asp Asn His Leu Pro Ile Ile Ser Ala Gly Ser Glu
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Glu Leu Pro Ser Pro Ser Ala Ser Ser Leu Gly Pro Ile Leu Pro Pro

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Leu Pro Gly Asp Asp Ser Pro Thr Thr Leu Cys Ser Phe Phe Pro Arg

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50 55 60

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	100 105 110
15	Lys Leu Ser Gly Gly Gly Gly Arg Arg Thr Arg Val Glu Gly Gly Gln
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	Leu Gly Gly Glu Glu Trp Thr Arg His Gly Ser Phe Val Asn Lys Pro
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	Thr Arg Gly Trp Leu His Pro Asn Asp Lys Val Met Gly Pro Gly Val
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	Ser Tyr Leu Val Arg Tyr Met Gly Cys Val Glu Val Leu Gln Ser Met
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	Arg Lys Pro Cys Ser Arg Pro Leu Ser Ser Ile Leu Gly Arg Ser Asn
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	Leu Lys Phe Ala Gly Met Pro Ile Thr Leu Thr Val Ser Thr Ser Ser
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	Leu Asn Leu Met Ala Ala Asp Cys Lys Gln Ile Ile Ala Asn His His
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	260 265 270
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	Glu	Leu	Arg	Phe
	Lys	Gln	Tyr	Leu
	Arg	Asn	Pro	Pro
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15	Lys	Leu	Val	Thr
	Pro	His	Asp	Arg
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	Asp	Gly	Ser	Ala
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	Glu	Val	Arg	Lys
	Gln	Met	Pro	Pro
	Pro	Pro	Pro	Pro
	Cys			
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	Leu	Phe	Asp	Asp
	Pro	Ser	Tyr	Val
	Asn	Val	Gln	Asn
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	Arg	Gln	Ala	Val
	Gly	Gly	Ala	Gly
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	Pro			
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	Ser	Ala	Pro	Arg
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	Met	Lys	Pro	Phe
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	Arg	Val	Pro	Pro
	Pro	Pro	Pro	Gln
	Ser	Val	Ser	Met
	Ala			
	465	470	475	480
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	Gly	Glu	Pro	Trp
	Phe	His	Gly	Lys
	Leu	Ser	Arg	Arg

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15	Gln Pro Lys His Leu Leu Leu Val Asp Pro Glu Gly Val Val Arg Thr			
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	Ser Glu Ile Ile Ser Tyr Trp Gly Phe Pro Ser Glu Glu Tyr Leu Val			
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20	Glu Thr Glu Asp Gly Tyr Ile Leu Cys Leu Asn Arg Ile Pro His Gly			
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25	agg aag aac cat tct gac aaa ggt ccc aaa cca gtt gtc ttc ctg caa			295
	Arg Lys Asn His Ser Asp Lys Gly Pro Lys Pro Val Val Phe Leu Gln			
	70	75	80	85
30	cat ggc ttg ctg gca gat tct agt aac tgg gtc aca aac ctt gcc aac			343
	His Gly Leu Leu Ala Asp Ser Ser Asn Trp Val Thr Asn Leu Ala Asn			
	90	95	100	
35	agc agc ctg ggc ttc att ctt gct gat gct ggt ttt gac gtg tgg atg			391
	Ser Ser Leu Gly Phe Ile Leu Ala Asp Ala Gly Phe Asp Val Trp Met			
40	105	110	115	
	ggc aac agc aga gga aat acc tgg tct cgg aaa cat aag aca ctc tca			439
	Gly Asn Ser Arg Gly Asn Thr Trp Ser Arg Lys His Lys Thr Leu Ser			
45	120	125	130	
	glt tct cag gat gaa ttc tgg gct ttc agt tat gat gag atg gca aaa			487
50	Val Ser Gln Asp Glu Phe Trp Ala Phe Ser Tyr Asp Glu Met Ala Lys			
	135	140	145	
55	tat gac cta cca gct tcc att aac ttc att ctg aat aaa act ggc caa			535
	Tyr Asp Leu Pro Ala Ser Ile Asn Phe Ile Leu Asn Lys Thr Gly Gln			

	150	155	160	165	
5	gaa caa gtg tai tai gtg ggt cat tct caa ggc acc act ala ggt ttt				583
	Glu Gln Val Tyr Tyr Val Gly His Ser Gln Gly Thr Thr Ile Gly Phe				
10	170	175	180		
	ata gca ttt tca cag atc cct gag ctg gct aaa agg att aaa atg ttt				631
15	Ile Ala Phe Ser Gln Ile Pro Glu Leu Ala Lys Arg Ile Lys Met Phe				
	185	190	195		
	ttt gcc ctg ggt cct gtg gct tcc glc gcc ttc tgt act agc cct atg				679
20	Phe Ala Leu Gly Pro Val Ala Ser Val Ala Phe Cys Thr Ser Pro Met				
	200	205	210		
25	gcc aaa tta gga cga tta cca gat cat ctc att aag gac tta ttt gga				727
	Ala Lys Leu Gly Arg Leu Pro Asp His Leu Ile Lys Asp Leu Phe Gly				
	215	220	225		
30	gac aaa gaa ttt ctt ccc cag agt gcg ttt ttg aag tgg ctg ggt acc				775
	Asp Lys Glu Phe Leu Pro Gln Ser Ala Phe Leu Lys Trp Leu Gly Thr				
35	230	235	240	245	
	cac gtt tgc act cat gtc ata ctg aag gag ctc tgt gga aat ctc tgt				823
	His Val Cys Thr His Val Ile Leu Lys Glu Leu Cys Gly Asn Leu Cys				
40	250	255	260		
	ttt ctt ctg tgt gga ttt aat gag aga aat tta aat atg tct aga gtg				871
45	Phe Leu Leu Cys Gly Phe Asn Glu Arg Asn Leu Asn Met Ser Arg Val				
	265	270	275		
	gat gla tat aca aca cat tct cct gct gga act tct gtg caa aac atg				919
50	Asp Val Tyr Thr Thr His Ser Pro Ala Gly Thr Ser Val Gln Asn Met				
	280	285	290		
55	tta cac tgg agc cag gct gtt aaa ttc caa aag ttt caa gcc ttt gac				967

Leu His Trp Ser Gln Ala Val Lys Phe Gln Lys Phe Gln Ala Phe Asp
 5 295 300 305
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 Trp Gly Ser Ser Ala Lys Asn Tyr Phe His Tyr Asn Gln Ser Tyr Pro
 10 310 315 320 325
 ccc aca tac aat glg aag gac atg ctt gtg ccg act gca gtc tgg agc 1063
 Pro Thr Tyr Asn Val Lys Asp Met Leu Val Pro Thr Ala Val Trp Ser
 15 330 335 340
 ggg ggt cac gac tgg ctt gca gat gtc tac gac gtc aat atc tta ctg 1111
 Gly Gly His Asp Trp Leu Ala Asp Val Tyr Asp Val Asn Ile Leu Leu
 20 345 350 355
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 Thr Gln Ile Thr Asn Leu Val Phe His Glu Ser Ile Pro Glu Trp Glu
 25 360 365 370
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 His Leu Asp Phe Ile Trp Gly Leu Asp Ala Pro Trp Arg Leu Tyr Asn
 30 375 380 385
 aaa att att aat cta atg agg aaa tat cag tgaaagctgg acttgagctg 1257
 Lys Ile Ile Asn Leu Met Arg Lys Tyr Gln
 35 390 395
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 35 40 45
 55 Glu Glu Tyr Leu Val Glu Thr Glu Asp Gly Tyr Ile Leu Cys Leu Asn

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	50	55	60	
5	Arg Ile Pro His Gly Arg Lys Asn His Ser Asp Lys Gly Pro Lys Pro			
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10	Val Val Phe Leu Gln His Gly Leu Leu Ala Asp Ser Ser Asn Trp Val			
	85	90	95	
15	Thr Asn Leu Ala Asn Ser Ser Leu Gly Phe Ile Leu Ala Asp Ala Gly			
	100	105	110	
	Phe Asp Val Trp Met Gly Asn Ser Arg Gly Asn Thr Trp Ser Arg Lys			
20	115	120	125	
	His Lys Thr Leu Ser Val Ser Gln Asp Glu Phe Trp Ala Phe Ser Tyr			
25	130	135	140	
	Asp Glu Met Ala Lys Tyr Asp Leu Pro Ala Ser Ile Asn Phe Ile Leu			
	145	150	155	160
30	Asn Lys Thr Gly Gln Glu Gln Val Tyr Tyr Val Gly His Ser Gln Gly			
	165	170	175	
35	Thr Thr Ile Gly Phe Ile Ala Phe Ser Gln Ile Pro Glu Leu Ala Lys			
	180	185	190	
	Arg Ile Lys Met Phe Phe Ala Leu Gly Pro Val Ala Ser Val Ala Phe			
40	195	200	205	
	Cys Thr Ser Pro Met Ala Lys Leu Gly Arg Leu Pro Asp His Leu Ile			
45	210	215	220	
	Lys Asp Leu Phe Gly Asp Lys Glu Phe Leu Pro Gln Ser Ala Phe Leu			
	225	230	235	240
50	Lys Trp Leu Gly Thr His Val Cys Thr His Val Ile Leu Lys Glu Leu			
	245	250	255	
55	Cys Gly Asn Leu Cys Phe Leu Leu Cys Gly Phe Asn Glu Arg Asn Leu			

	260	265	270
5	Asn Met Ser Arg Val Asp Val Tyr Thr Thr His Ser Pro Ala Gly Thr		
	275	280	285
10	Ser Val Gln Asn Met Leu His Trp Ser Gln Ala Val Lys Phe Gln Lys		
	290	295	300
	Phe Gln Ala Phe Asp Trp Gly Ser Ser Ala Lys Asn Tyr Phe His Tyr		
15	305	310	315
	Asn Gln Ser Tyr Pro Pro Thr Tyr Asn Val Lys Asp Met Leu Val Pro		
20	325	330	335
	Thr Ala Val Trp Ser Gly Gly His Asp Trp Leu Ala Asp Val Tyr Asp		
	340	345	350
25	Val Asn Ile Leu Leu Thr Gln Ile Thr Asn Leu Val Phe His Glu Ser		
	355	360	365
30	Ile Pro Glu Trp Glu His Leu Asp Phe Ile Trp Gly Leu Asp Ala Pro		
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 Gly Arg Ala Thr His Ala Val Val Arg Ala Leu Pro Glu Ser Leu Gly
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 30 30 35 40
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 Gly Leu Gln Val Val Glu Leu Pro Ala Asp Glu Ser Leu Pro Asp Cys
 40 60 65 70
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 Val Phe Val Glu Asp Val Ala Val Val Cys Glu Glu Thr Ala Leu Ile
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 95 100 105
 gaa gca tta gaa aaa ctt cag ctc aat ata gla gag atg aaa gat gaa 688
 55 Glu Ala Leu Glu Lys Leu Gln Leu Asn Ile Val Glu Met Lys Asp Glu

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	Asn Ala Thr Leu Asp Gly Gly Asp Val Leu Phe Thr Gly Arg Glu Phe			
10	125	130	135	
	ttt gtg ggc ctt tcc aaa agg aca aat caa cga ggt gct gaa atc ttg	784		
15	Phe Val Gly Leu Ser Lys Arg Thr Asn Gln Arg Gly Ala Glu Ile Leu			
	140	145	150	
20	gct gat act ttt aag gac tat gca gtc tcc aca gtg cca gtg gca gat	832		
	Ala Asp Thr Phe Lys Asp Tyr Ala Val Ser Thr Val Pro Val Ala Asp			
	155	160	165	170
25	ggg ttg cat ttg aag agt ttc tgc agc atg gct ggg cct aac ctg atc	880		
	Gly Leu His Leu Lys Ser Phe Cys Ser Met Ala Gly Pro Asn Leu Ile			
	175	180	185	
30	gca att ggg tct agt gaa tct gca cag aag gcc ctt aag atc atg caa	928		
	Ala Ile Gly Ser Ser Glu Ser Ala Gln Lys Ala Leu Lys Ile Met Gln			
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	cag atg agt gac cac cgc tac gac aaa ctc act gtg cct gat gac ata	976		
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	205	210	215	
45	gca gca aac tgt ata tat cta aat atc ccc aac aaa ggg cac gtc ttg	1024		
	Ala Ala Asn Cys Ile Tyr Leu Asn Ile Pro Asn Lys Gly His Val Leu			
	220	225	230	
50	ctg cac cga acc ccg gaa gag tat cca gaa agt gca aag gtt tat gag	1072		
	Leu His Arg Thr Pro Glu Glu Tyr Pro Glu Ser Ala Lys Val Tyr Glu			
	235	240	245	250
55	aaa ctg aag gac cat atg ctg atc ccc gtg agc atg tct gaa ctg gaa	1120		

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Lys Leu Lys Asp His Met Leu Ile Pro Val Ser Met Ser Glu Leu Glu
5 255 260 265
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Lys Val Asp Gly Leu Leu Thr Cys Cys Ser Val Leu Ile Asn Lys Lys
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gta gac tcc tgagctgcag agtccccccc ggtagccggc aagaccgcac 1217
15 Val Asp Ser
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55 35 40 45

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	Gly	Asp	Val	Leu	Phe	Thr	Gly	Arg	Glu	Phe	Phe	Val	Gly	Leu	Ser	Lys
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									130							140
	Arg	Thr	Asn	Gln	Arg	Gly	Ala	Glu	Ile	Leu	Ala	Asp	Thr	Phe	Lys	Asp
30									145							160
	Tyr	Ala	Val	Ser	Thr	Val	Pro	Val	Ala	Asp	Gly	Leu	His	Leu	Lys	Ser
									165							175
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	Phe	Cys	Ser	Met	Ala	Gly	Pro	Asn	Leu	Ile	Ala	Ile	Gly	Ser	Ser	Glu
									180							190
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	Ser	Ala	Gln	Lys	Ala	Leu	Lys	Ile	Met	Gln	Gln	Met	Ser	Asp	His	Arg
									195							205
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	Tyr	Asp	Lys	Leu	Thr	Val	Pro	Asp	Asp	Ile	Ala	Ala	Asn	Cys	Ile	Tyr
									210							220
50																
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									225							240
	Glu	Tyr	Pro	Glu	Ser	Ala	Lys	Val	Tyr	Glu	Lys	Leu	Lys	Asp	His	Met
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	Leu	Ile	Pro	Val	Ser	Met	Ser	Glu	Leu	Glu	Lys	Val	Asp	Gly	Leu	Leu

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 Lys Phe Gln His Pro Gly Ser Asp Met Arg Gln Glu Lys Pro Ser Ser
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 30 35 40
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 55 gtg ctg acg ctg ctg gac aag ctg glg aac atg cta gac gct glg cag 365

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5 Val Leu Thr Leu Leu Asp Lys Leu Val Asn Met Leu Asp Ala Val Gln
 60 65 70
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 10 Glu Asn Gln His Lys Met Glu Gln Arg Gln Ile Ser Leu Glu Gly Ser
 75 80 85
 15 gtg aag ggc atc cag aat gac ctc acc aag ctc tcc aag tac cag gcc 461
 Val Lys Gly Ile Gln Asn Asp Leu Thr Lys Leu Ser Lys Tyr Gln Ala
 90 95 100 105
 20 tcc acc agc aac acg gig agc aag ctg ctg gag aag tcc cgc aag gtc 509
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 25 110 115 120
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 30 125 130 135
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 220 225 230
 15 tcc agc ctg aag aaa gtg gat agc ctc aag aaa gca ttt tct cgc cag 893
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 20 aac atc gag aaa aag atg aac aag ctg ggg aca aag atc gta tct gta 941
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 40 ggg cgg aag aaa gtc cga gag gga gaa agc cat gca gaa aat gag acc 1085
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 55 330 335 340 345

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15 Glu Asp Glu Glu Glu Glu Ser Val Ala Leu Glu Gln Ala Gln Lys Val
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20 Arg Tyr Glu Gly Ser Tyr Ala Leu Thr Ser Glu Glu Ala Glu Arg Ser
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20	Leu Val Asn Met Leu Asp Ala Val Gln Glu Asn Gln His Lys Met Glu			
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	Gln Arg Gln Ile Ser Leu Glu Gly Ser Val Lys Gly Ile Gln Asn Asp			
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	Leu Thr Lys Leu Ser Lys Tyr Gln Ala Ser Thr Ser Asn Thr Val Ser			
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35	Lys Glu Arg Met Asp Arg Gln Cys Ala Gln Val Lys Arg Leu Glu Asn			
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40	Asn His Ala Gln Leu Leu Arg Arg Asn His Phe Lys Val Leu Ile Phe			
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	Ser Gly Ala Val Glu Gly Lys Glu Glu Leu Pro Asp Glu Asn Lys Ser			
50		180	185	190
	Leu Glu Glu Thr Leu His Thr Val Asp Leu Ser Ser Asp Asp Asp Leu			
55		195	200	205

Pro His Asp Glu Glu Ala Leu Glu Asp Ser Ala Glu Glu Lys Val Glu
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	Cys Tyr Gly His Ala Ser Glu Cys Ala Pro Val Asp Gly Phe Asn Glu	
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	gaa gtc gaa gga atg gtt cac gga cac tgc atg tgc agg cat aac acc	1029
55	Glu Val Glu Gly Met Val His Gly His Cys Met Cys Arg His Asn Thr	
	290 295 300	

5 aag ggc tta aac tgt gaa ctc tgc atg gat ttc tac cat gat tta cct 1077
 Lys Gly Leu Asn Cys Glu Leu Cys Met Asp Phe Tyr His Asp Leu Pro
 305 310 315 320
 10 tgg aga cct gct gaa ggc cga aac agc aac gcc tgt aaa aaa tgt aac 1125
 Trp Arg Pro Ala Glu Gly Arg Asn Ser Asn Ala Cys Lys Lys Cys Asn
 15 325 330 335
 tgc aat gaa cat tcc atc tct tgt cac ttt gac atg gct gtt tac ctg 1173
 Cys Asn Glu His Ser Ile Ser Cys His Phe Asp Met Ala Val Tyr Leu
 20 340 345 350
 gcc acg ggg aac gtc agc gga ggc gtc tgt gat gac tgt cag cac aac 1221
 25 Ala Thr Gly Asn Val Ser Gly Gly Val Cys Asp Asp Cys Gln His Asn
 355 360 365
 acc atg ggg cgc aac tgt gag cag tgc aag ccg ttt tac tac cag cac 1269
 30 Thr Met Gly Arg Asn Cys Glu Gln Cys Lys Pro Phe Tyr Tyr Gln His
 370 375 380
 35 cca gag agg gac atc cga gat cct aat ttc tgt gaa cga tgt acg tgt 1317
 Pro Glu Arg Asp Ile Arg Asp Pro Asn Phe Cys Glu Arg Cys Thr Cys
 385 390 395 400
 40 gac cca gct ggc tct caa aat gag gga att tgt gac agc tat act gat 1365
 Asp Pro Ala Gly Ser Gln Asn Glu Gly Ile Cys Asp Ser Tyr Thr Asp
 45 405 410 415
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 50 Phe Ser Thr Gly Leu Ile Ala Gly Gln Cys Arg Cys Lys Leu Asn Val
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 55 Glu Gly Glu His Cys Asp Val Cys Lys Glu Gly Phe Tyr Asp Leu Ser

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	Ser Glu Asp Pro Phe Gly Cys Lys Ser Cys Ala Cys Asn Pro Leu Gly			
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	aca att cct gga ggg aat cct tgt gat tcc gag aca ggt cac tgc tac	1557		
	Thr Ile Pro Gly Gly Asn Pro Cys Asp Ser Glu Thr Gly His Cys Tyr			
15	465	470	475	480
	tgc aag cgt ctg gtg aca gga cag cat tgt gac cag tgc ctg cca gag	1605		
20	Cys Lys Arg Leu Val Thr Gly Gln His Cys Asp Gln Cys Leu Pro Glu			
	485	490	495	
25	cac tgg ggc tta agc aat gat ttg gat gga tgt cga cca tgt gac tgt	1653		
	His Trp Gly Leu Ser Asn Asp Leu Asp Gly Cys Arg Pro Cys Asp Cys			
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30	gac ctt ggg gga gcc tta aac aac agt tgc ttt gcg gag tca ggc cag	1701		
	Asp Leu Gly Gly Ala Leu Asn Asn Ser Cys Phe Ala Glu Ser Gly Gln			
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35	tgc tca tgc cgg cct cac atg att gga cgt cag tgc aac gaa gtg gaa	1749		
	Cys Ser Cys Arg Pro His Met Ile Gly Arg Gln Cys Asn Glu Val Glu			
40	530	535	540	
	cct ggt tac tac ttt gcc acc ctg gat cac tac ctc tat gaa gcg gag	1797		
	Pro Gly Tyr Tyr Phe Ala Thr Leu Asp His Tyr Leu Tyr Glu Ala Glu			
45	545	550	555	560
	gaa gcc aac ttg ggg cct ggg gtt agc ata glg gag cgg caa tat atc	1845		
50	Glu Ala Asn Leu Gly Pro Gly Val Ser Ile Val Glu Arg Gln Tyr Ile			
	565	570	575	
55	cag gac cgg att ccc tcc tgg act gga gcc ggc ttc gtc cga glg cct	1893		
	Gln Asp Arg Ile Pro Ser Trp Thr Gly Ala Gly Phe Val Arg Val Pro			

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	Glu Gly Ala Tyr Leu Glu Phe Phe Ile Asp Asn Ile Pro Tyr Ser Met			
10	595	600	605	
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	Glu Tyr Asp Ile Leu Ile Arg Tyr Glu Pro Gln Leu Pro Asp His Trp			
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20	Glu Lys Ala Val Ile Thr Val Gln Arg Pro Gly Arg Ile Pro Thr Ser			
	625	630	635	640
25	agc cga tgt ggt aat acc atc ccc gat gat gac aac cag gtg gtg tca			2085
	Ser Arg Cys Gly Asn Thr Ile Pro Asp Asp Asp Asn Gln Val Val Ser			
	645	650	655	
30	tta tca cca ggc tca aga tat gtc gtc ctt cct cgg ccg gtg tgc ttt			2133
	Leu Ser Pro Gly Ser Arg Tyr Val Val Leu Pro Arg Pro Val Cys Phe			
35	660	665	670	
	gag aag gga aca aac tac acg gtg agg ttg gag ctg cct cag tac acc			2181
	Glu Lys Gly Thr Asn Tyr Thr Val Arg Leu Glu Leu Pro Gln Tyr Thr			
40	675	680	685	
	tcc tct gat agc gac gtg gag agc ccc tac acg ctg atc gat tct ctt			2229
45	Ser Ser Asp Ser Asp Val Glu Ser Pro Tyr Thr Leu Ile Asp Ser Leu			
	690	695	700	
50	glt ctc atg cca tac tgt aaa tca ctg gac atc ttc acc gtg gga ggt			2277
	Val Leu Met Pro Tyr Cys Lys Ser Leu Asp Ile Phe Thr Val Gly Gly			
	705	710	715	720
55	tca gga gat ggg gtg gtc acc aac agt gcc tgg gaa acc ttt cag aga			2325

	Ser Gly Asp Gly Val Val Thr Asn Ser Ala Trp Glu Thr Phe Gln Arg	
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10	Tyr Arg Cys Leu Glu Asn Ser Arg Ser Val Val Lys Thr Pro Met Thr	
	740 745 750	
	gat gtt tgc aga aac atc atc ttt agc att tct gcc ctg tta cac cag	2421
15	Asp Val Cys Arg Asn Ile Ile Phe Ser Ile Ser Ala Leu Leu His Gln	
	755 760 765	
20	aca ggc ctg gct tgt gaa tgc gac cct cag ggt tgc tta agt tcc gtg	2469
	Thr Gly Leu Ala Cys Glu Cys Asp Pro Gln Gly Ser Leu Ser Ser Val	
	770 775 780	
25	tgt gat_ccc aac gga ggc cag tgc cag tgc cgg ccc aac glg gtl gga	2517
	Cys Asp Pro Asn Gly Gly Gln Cys Gln Cys Arg Pro Asn Val Val Gly	
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40	Gly Cys Lys Pro Cys Glu Cys His Leu Gln Gly Ser Val Asn Ala Phe	
	820 825 830	
	tgc aat ccc gtc act ggc cag tgc cac tgt ttc cag gga glg tat gct	2661
45	Cys Asn Pro Val Thr Gly Gln Cys His Cys Phe Gln Gly Val Tyr Ala	
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50	cgg cag tgt gat cgg tgc tta cct ggg cac tgg ggc ttt cca agt tgc	2709
	Arg Gln Cys Asp Arg Cys Leu Pro Gly His Trp Gly Phe Pro Ser Cys	
	850 855 860	
55	cag ccc tgc cag tgc aat ggc cac gcc gat gac tgc gac cca glg act	2757

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	Gln Pro Cys Gln Cys Asn Gly His Ala Asp Asp Cys Asp Pro Val Thr	
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10	Gly Glu Cys Leu Asn Cys Gln Asp Tyr Thr Met Gly His Asn Cys Glu	
	885 890 895	
	agg tgc ttg gct ggt tac tat ggc gac ccc atc att ggg tca ggt gat	2853
15	Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp	
	900 905 910	
20	cac tgc cgc cct tgc cct tgc cca gat ggt ccc gac agt gga cgc cag	2901
	His Cys Arg Pro Cys Pro Cys Pro Asp Gly Pro Asp Ser Gly Arg Gln	
	915 920 925	
25	ttt gcc agg agc tgc tac caa gat cct gtt act tta cag ctt gcc tgt	2949
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30	930 935 940	
	glt tgt gat cct gga tac att ggt tcc aga tgt gac gac tgt gcc tca	2997
35	Val Cys Asp Pro Gly Tyr Ile Gly Ser Arg Cys Asp Asp Cys Ala Ser	
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40	Gly Tyr Phe Gly Asn Pro Ser Glu Val Gly Gly Ser Cys Gln Pro Cys	
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45	cag tgt cac aac aac att gac acg aca gac cca gaa gcc tgt gac aag	3093
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	980 985 990	
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 Cys Arg Lys Cys Val Cys Asn Tyr Leu Gly Thr Val Gln Glu His Cys
 1025 1030 1035 1040
 15 aac ggc tct gac tgc cag tgc gac aaa gcc act ggt cag tgc ttg tgt 3285
 Asn Gly Ser Asp Cys Gln Cys Asp Lys Ala Thr Gly Gln Cys Leu Cys
 1045 1050 1055
 20 ctt cct aat gtg atc ggg cag aac tgt gac cgc tgt gcg ccc aat acc 3333
 Leu Pro Asn Val Ile Gly Gln Asn Cys Asp Arg Cys Ala Pro Asn Thr
 25 1060 1065 1070
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 Trp Gln Leu Ala Ser Gly Thr Gly Cys Asp Pro Cys Asn Cys Asn Ala
 1075 1080 1085
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 Ala His Ser Phe Gly Pro Ser Cys Asn Glu Phe Thr Gly Gln Cys Gln
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 Phe Trp Gly Asp Pro Asp Val Glu Cys Arg Ala Cys Asp Cys Asp Pro
 1125 1130 1135
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 20 1185 1190 1195 1200
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	gat att cgg ggt gcc ttg gat agc att acc aag tat ttc cag atg tct			4101
	Asp Ile Arg Gly Ala Leu Asp Ser Ile Thr Lys Tyr Phe Gln Met Ser			
15	1315	1320	1325	
	ctt gag gca gag gag agg gtg aat gcc tcc acc aca gaa ccc aac agc			4149
20	Leu Glu Ala Glu Glu Arg Val Asn Ala Ser Thr Thr Glu Pro Asn Ser			
	1330	1335	1340	
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	Thr Val Glu Gln Ser Ala Leu Met Arg Asp Arg Val Glu Asp Val Met			
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30	atg gag cga gaa tcc cag ttc aag gaa aaa caa gag gag cag gct cgc			4245
	Met Glu Arg Glu Ser Gln Phe Lys Glu Lys Gln Glu Glu Gln Ala Arg			
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	Leu Leu Asp Glu Leu Ala Gly Lys Leu Gln Ser Leu Asp Leu Ser Ala			
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45	1395	1400	1405	
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50	Thr Glu Cys Gly Gly Pro Asn Cys Arg Thr Asp Glu Gly Glu Arg Lys			
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55	tgt ggg ggg cct ggc tgt ggt ggt ctg gtt act gtt gca cac aac gcc			4437
	Cys Gly Gly Pro Gly Cys Gly Gly Leu Val Thr Val Ala His Asn Ala			

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10		1445	1450	1455	
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	Glu Val Glu Gln Leu Ser Lys Met Val Ser Glu Ala Lys Leu Arg Ala				
15		1460	1465	1470	
	gat gag gca aaa caa agt gct gaa gac att ctg ttg aag aca aat gct				4581
20	Asp Glu Ala Lys Gln Ser Ala Glu Asp Ile Leu Leu Lys Thr Asn Ala				
		1475	1480	1485	
25	acc aaa gaa aaa atg gac aag agc aat gag gag ctg aga aat cta atc				4629
	Thr Lys Glu Lys Met Asp Lys Ser Asn Glu Glu Leu Arg Asn Leu Ile				
		1490	1495	1500	
30	aag caa atc aga aac ttt ttg acc cag gat agt gct gat ttg gac agc				4677
	Lys Gln Ile Arg Asn Phe Leu Thr Gln Asp Ser Ala Asp Leu Asp Ser				
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35 1650 1655 1660
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20 25 30
55 Gly Ser Cys Tyr Pro Ala Thr Gly Asp Leu Leu Ile Gly Arg Ala Gln

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	35	40	45													
5	Lys	Leu	Ser	Val	Thr	Ser	Thr	Cys	Gly	Leu	His	Lys	Pro	Glu	Pro	Tyr
	50	55	60													
10	Cys	Ile	Val	Ser	His	Leu	Gln	Glu	Asp	Lys	Lys	Cys	Phe	Ile	Cys	Asn
	65	70	75	80												
	Ser	Gln	Asp	Pro	Tyr	His	Glu	Thr	Leu	Asn	Pro	Asp	Ser	His	Leu	Ile
15		85	90	95												
	Glu	Asn	Val	Val	Thr	Thr	Phe	Ala	Pro	Asn	Arg	Leu	Lys	Ile	Trp	Trp
20		100	105	110												
	Gln	Ser	Glu	Asn	Gly	Val	Glu	Asn	Val	Thr	Ile	Gln	Leu	Asp	Leu	Glu
	115	120	125													
25	Ala	Glu	Phe	His	Phe	Thr	His	Leu	Ile	Met	Thr	Phe	Lys	Thr	Phe	Arg
	130	135	140													
30	Pro	Ala	Ala	Met	Leu	Ile	Glu	Arg	Ser	Ser	Asp	Phe	Gly	Lys	Thr	Trp
	145	150	155	160												
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35		165	170	175												
	Ile	Ser	Thr	Gly	Pro	Met	Lys	Lys	Val	Asp	Asp	Ile	Ile	Cys	Asp	Ser
40		180	185	190												
	Arg	Tyr	Ser	Asp	Ile	Glu	Pro	Ser	Thr	Glu	Gly	Glu	Val	Ile	Phe	Arg
45		195	200	205												
	Ala	Leu	Asp	Pro	Ala	Phe	Lys	Ile	Glu	Asp	Pro	Tyr	Ser	Pro	Arg	Ile
	210	215	220													
50	Gln	Asn	Leu	Leu	Lys	Ile	Thr	Asn	Leu	Arg	Ile	Lys	Phe	Val	Lys	Leu
	225	230	235	240												
55	His	Thr	Leu	Gly	Asp	Asn	Leu	Leu	Asp	Ser	Arg	Met	Glu	Ile	Arg	Glu

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	245	250	255
5	Lys Tyr Tyr Tyr Ala Val Tyr Asp Met Val Val Arg Gly Asn Cys Phe		
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10	Cys Tyr Gly His Ala Ser Glu Cys Ala Pro Val Asp Gly Phe Asn Glu		
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	Glu Val Glu Gly Met Val His Gly His Cys Met Cys Arg His Asn Thr		
15	290	295	300
	Lys Gly Leu Asn Cys Glu Leu Cys Met Asp Phe Tyr His Asp Leu Pro		
	305	310	315
20	Trp Arg Pro Ala Glu Gly Arg Asn Ser Asn Ala Cys Lys Lys Cys Asn		
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25	Cys Asn Glu His Ser Ile Ser Cys His Phe Asp Met Ala Val Tyr Leu		
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30	Ala Thr Gly Asn Val Ser Gly Gly Val Cys Asp Asp Cys Gln His Asn		
	355	360	365
	Thr Met Gly Arg Asn Cys Glu Gln Cys Lys Pro Phe Tyr Tyr Gln His		
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	Pro Glu Arg Asp Ile Arg Asp Pro Asn Phe Cys Glu Arg Cys Thr Cys		
	385	390	395
40	Asp Pro Ala Gly Ser Gln Asn Glu Gly Ile Cys Asp Ser Tyr Thr Asp		
	405	410	415
45	Phe Ser Thr Gly Leu Ile Ala Gly Gln Cys Arg Cys Lys Leu Asn Val		
	420	425	430
50	Glu Gly Glu His Cys Asp Val Cys Lys Glu Gly Phe Tyr Asp Leu Ser		
	435	440	445
	Ser Glu Asp Pro Phe Gly Cys Lys Ser Cys Ala Cys Asn Pro Leu Gly		
55	450	455	460

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 5 465 470 475 480
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 10 485 490 495
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 15 Asp Leu Gly Gly Ala Leu Asn Asn Ser Cys Phe Ala Glu Ser Gly Gln
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 625 630 635 640
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 Leu Ser Pro Gly Ser Arg Tyr Val Val Leu Pro Arg Pro Val Cys Phe
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[illegible]

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	Gly Tyr Phe Gly Asn Pro Ser Glu Val Gly Gly Ser Cys Gln Pro Cys		
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	Asn Gly Ser Asp Cys Gln Cys Asp Lys Ala Thr Gly Gln Cys Leu Cys		
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	Leu Pro Asn Val Ile Gly Gln Asn Cys Asp Arg Cys Ala Pro Asn Thr		
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	Trp Gln Leu Ala Ser Gly Thr Gly Cys Asp Pro Cys Asn Cys Asn Ala		
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	Arg Gly Ile Glu Thr Pro Gln Cys Asp Gln Ser Thr Gly Gln Cys Val			
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	Cys Val Glu Gly Val Glu Gly Pro Arg Cys Asp Lys Cys Thr Arg Gly			
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20	Tyr Ser Gly Val Phe Pro Asp Cys Thr Pro Cys His Gln Cys Phe Ala			
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25	Leu Trp Asp Val Ile Ile Ala Glu Leu Thr Asn Arg Thr His Arg Phe			
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	Leu Phe Glu Glu Ala Glu Lys Leu Ile Lys Asp Val Thr Glu Met Met			
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	Asn Thr Val Lys Glu Leu Ala Glu Gln Leu Glu Phe Ile Lys Asn Ser			
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	Ala Glu Ser Leu Ala Arg Pro Cys Ala Pro Gly Ala Pro Ala Glu Ala	
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	Arg Ala Asp Leu His Ala Val Gln Gly Trp Ala Ala Arg Ser Trp Leu	
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	Pro Ala Gly Cys Glu Thr Ala Ile Leu Phe Pro Met Arg Ser Lys Lys	
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	Ser Ala Cys Ile Trp Val Lys Ala Thr Asp Val Leu Asn Lys Thr Ile	
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20	ctc agc tac caa tcc ata gtg ttt gtg gtg ggt gga gag gag aac aaa	770
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35	ggc acc tgg aat tca gag gaa ggg ctc aca tcc ttg tgg gla aat ggt	866
	Gly Thr Trp Asn Ser Glu Glu Gly Leu Thr Ser Leu Trp Val Asn Gly	
	275 280 285	
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	Glu Leu Ala Ala Thr Thr Val Glu Met Ala Thr Gly His Ile Val Pro	
	290 295 300	
45	gag gga gga atc ctg cag att ggc caa gaa aag aat ggc tgc tgt glg	962
	Glu Gly Gly Ile Leu Gln Ile Gly Gln Glu Lys Asn Gly Cys Cys Val	
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	ggt ggt ggc ttt gat gaa aca tta gcc ttc tct ggg aga ctc aca ggc	1010
	Gly Gly Gly Phe Asp Glu Thr Leu Ala Phe Ser Gly Arg Leu Thr Gly	
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10	Glu Ile Asp Asn Gly Leu His Pro Thr	Glu Asp Pro Thr	Pro Cys Ala	
	35	40	45	
15	Cys Gly Gln Glu His Ser Glu Trp Asp Lys	Leu Phe Ile Met	Leu Glu	
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20	Asn Ser Gln Met Arg Glu Arg Met Leu Leu	Gln Ala Thr Asp Asp	Val	
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	Leu Arg Gly Glu Leu Gln Arg Leu Arg Glu Glu	Leu Gly Arg Leu Ala		
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35	Arg Arg Leu Ala Arg Met Glu Gly Ala Glu	Ala Gln Arg Pro Glu Glu		
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40	Ala Gly Arg Ala Leu Ala Ala Val Leu Glu	Glu Leu Arg Gln Thr Arg		
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	Ala Asp Leu His Ala Val Gln Gly Trp Ala	Ala Arg Ser Trp Leu Pro		
	165	170	175	
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	180	185	190	
50	Phe Gly Ser Val His Pro Val Arg Pro Met	Arg Leu Glu Ser Phe Ser		
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55	Ala Cys Ile Trp Val Lys Ala Thr Asp Val	Leu Asn Lys Thr Ile Leu		

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	Ser Tyr Gln Ser Ile Val Phe Val Val Gly Gly Glu Glu Asn Lys Leu			
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	Val Ala Glu Ala Met Val Ser Leu Gly Arg Trp Thr His Leu Cys Gly			
15	260	265	270	
	Thr Trp Asn Ser Glu Glu Gly Leu Thr Ser Leu Trp Val Asn Gly Glu			
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25	Gly Gly Ile Leu Gln Ile Gly Gln Glu Lys Asn Gly Cys Cys Val Gly			
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	Asn Ile Trp Asp Ser Val Leu Ser Asn Glu Glu Ile Arg Glu Thr Gly			
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 Gly Gln Asn Cys Ser Gly Pro Cys Arg Cys Pro Asp Glu Pro Ala Pro
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 Arg Cys Pro Ala Gly Val Ser Leu Val Leu Asp Gly Cys Gly Cys Cys
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Cys Arg Cys Pro Asp Glu Pro Ala Pro Arg Cys Pro Ala Gly Val Ser

35 40 45

Leu Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu

50 55 60

Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu

65 70 75 80

	Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr
5	85 90 95
	Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly Thr Val Tyr Arg Ser
10	100 105 110
	Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp
15	115 120 125
	Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu Pro
	130 135 140
20	Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys
	145 150 155 160
25	Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln Thr Val Val Gly
	165 170 175
	Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro
30	180 185 190
	Thr Met Ile Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala
35	195 200 205
	Cys Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp
	210 215 220
40	Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
	225 230 235 240
45	Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
	245 250 255
	Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly
50	260 265 270
	Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr
55	275 280 285

Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu
 290 295 300
 5 Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Asn Met Met Phe Ile
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 Met Asp
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 ggg act att aag gag gct ctg tcg gtg gtg agc gac gac cag tcc ctc 226
 Gly Thr Ile Lys Glu Ala Leu Ser Val Val Ser Asp Asp Gln Ser Leu
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 55 Phe Asp Ser Ala Tyr Gly Ala Ala Ala His Leu Pro Lys Ala Asp Met

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5	act gcc tgc ggg agt cct gac tac ggg cag ccc cac aag atc aac ccc	322		
	Thr Ala Ser Gly Ser Pro Asp Tyr Gly Gln Pro His Lys Ile Asn Pro			
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10	ctc cca cca cag cag gag tgg atc aat cag cca gtc agg gtc aac gtc	370		
	Leu Pro Pro Gln Gln Glu Trp Ile Asn Gln Pro Val Arg Val Asn Val			
15	55	60	65	
	aag cgg gag tat gac cac atg aat gga tcc agg gag tct ccg gtc gac	418		
	Lys Arg Glu Tyr Asp His Met Asn Gly Ser Arg Glu Ser Pro Val Asp			
20	70	75	80	
	tgc agc gtt agc aaa tgc agc aag ctg gtc ggc gga ggc gag tcc aac	466		
25	Cys Ser Val Ser Lys Cys Ser Lys Leu Val Gly Gly Gly Glu Ser Asn			
	85	90	95	
30	ccc atg aac tac aac agc tat atg gac gag aag aat ggc ccc cct cct	514		
	Pro Met Asn Tyr Asn Ser Tyr Met Asp Glu Lys Asn Gly Pro Pro Pro			
	100	105	110	
35	ccc aac atg acc acc aac gag agg aga gtc atc gtc ccc gca gac ccc	562		
	Pro Asn Met Thr Thr Asn Glu Arg Arg Val Ile Val Pro Ala Asp Pro			
40	115	120	125	130
	aca ctg tgg aca cag gag cat gtc agg caa tgg ctg gag tgg gcc ata	610		
	Thr Leu Trp Thr Gln Glu His Val Arg Gln Trp Leu Glu Trp Ala Ile			
45	135	140	145	
	aag gag tac agc ttg atg gag atc gac aca tcc ttt ttc cag aac atg	658		
50	Lys Glu Tyr Ser Leu Met Glu Ile Asp Thr Ser Phe Phe Gln Asn Met			
	150	155	160	
55	gat ggc aag gaa ctg tgt aaa atg aac aag gag gac ttc ctc cgc gcc	706		
	Asp Gly Lys Glu Leu Cys Lys Met Asn Lys Glu Asp Phe Leu Arg Ala			

5 165 170 175
 acc acc ctc tac aac acg gaa gtg ctg ttg tca cac ctc agt tac ctc 754
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 10 180 185 190
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 Arg Glu Ser Ser Leu Leu Ala Tyr Asn Thr Thr Ser His Thr Asp Gln
 15 195 200 205 210
 tcc tca cga ttg agt gtc aaa gaa gac cct tct tat gac tca gtc aga 850
 Ser Ser Arg Leu Ser Val Lys Glu Asp Pro Ser Tyr Asp Ser Val Arg
 20 215 220 225
 aga gga gct tgg ggc aat aac atg aat tct ggc ctc aac aaa agt cct 898
 Arg Gly Ala Trp Gly Asn Asn Met Asn Ser Gly Leu Asn Lys Ser Pro
 25 230 235 240
 ccc ctt gga ggg gca caa acg atc agt aag aat aca gag caa cgg ccc 946
 Pro Leu Gly Gly Ala Gln Thr Ile Ser Lys Asn Thr Glu Gln Arg Pro
 30 245 250 255
 cag cca gat ccg tat cag atc ctg ggc ccg acc agc agt cgc cta gcc 994
 Gln Pro Asp Pro Tyr Gln Ile Leu Gly Pro Thr Ser Ser Arg Leu Ala
 35 260 265 270
 aac cct gga agc ggg cag atc cag ctg tgg caa ttc ctc ctg gag ctg 1042
 Asn Pro Gly Ser Gly Gln Ile Gln Leu Trp Gln Phe Leu Leu Glu Leu
 40 275 280 285 290
 ctc tcc gac agc gcc aac gcc agc tgt atc acc tgg gag ggg acc aac 1090
 Leu Ser Asp Ser Ala Asn Ala Ser Cys Ile Thr Trp Glu Gly Thr Asn
 45 295 300 305
 ggg gag ttc aaa atg acg gac ccc gat gag gtg gcc agg cgc tgg ggc 1138

Gly Glu Phe Lys Met Thr Asp Pro Asp Glu Val Ala Arg Arg Trp Gly
 5 310 315 320
 gag cgg aaa agc aag ccc aac atg aat tac gac aag ctg agc cgg gcc 1186
 Glu Arg Lys Ser Lys Pro Asn Met Asn Tyr Asp Lys Leu Ser Arg Ala
 10 325 330 335
 ctc cgt tat tac tat gat aaa aac att atg acc aaa gtg cac ggc aaa 1234
 15 Leu Arg Tyr Tyr Tyr Asp Lys Asn Ile Met Thr Lys Val His Gly Lys
 340 345 350
 20 aga tat gct tac aaa ttt gac ttc cac ggc att gcc cag gct ctg cag 1282
 Arg Tyr Ala Tyr Lys Phe Asp Phe His Gly Ile Ala Gln Ala Leu Gln
 355 360 365 370
 25 cca cat ccg acc gag tgg tcc atg tac aag tac cct tct gac atc tcc 1330
 Pro His Pro Thr Glu Ser Ser Met Tyr Lys Tyr Pro Ser Asp Ile Ser
 375 380 385
 30 tac atg cct tcc caa cat gcc cac cag cag aag gtg aac ttt gtc cct 1378
 Tyr Met Pro Ser Gln His Ala His Gln Gln Lys Val Asn Phe Val Pro
 35 390 395 400
 ccc cat cca tcc tcc atg cct gtc act tcc tcc agc ttc ttt gga gcc 1426
 40 Pro His Pro Ser Ser Met Pro Val Thr Ser Ser Ser Phe Phe Gly Ala
 405 410 415
 45 gca tca caa tac tgg acc tcc acg ggg gga atc tac ccc aac ccc aac 1474
 Ala Ser Gln Tyr Trp Thr Ser Thr Gly Gly Ile Tyr Pro Asn Pro Asn
 420 425 430
 50 gtc ccc cgc cat cct aac acc cac gtg cct tca cac tta ggc agc tac 1522
 Val Pro Arg His Pro Asn Thr His Val Pro Ser His Leu Gly Ser Tyr
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 55 tac tagaagctta ctcatcagtg gcccttctagc tgaagcccat cctgcacact 1575

Tyr

5 tactggatgc ttgggacica acaggacata lgtggccttg aagggaagac aaaactggat 1635
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 25 aagaaatitt aatgcaata catacatlcc tgaagacgg ggaattaaat tactaatttt 2235
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<211> 451

<212> PRT

<213> Homo sapiens

<400> 84

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20 25 30

20 Asp Met Thr Ala Ser Gly Ser Pro Asp Tyr Gly Gln Pro His Lys Ile
35 40 45

25 Asn Pro Leu Pro Pro Gln Gln Glu Trp Ile Asn Gln Pro Val Arg Val
50 55 60

30 Asn Val Lys Arg Glu Tyr Asp His Met Asn Gly Ser Arg Glu Ser Pro
65 70 75 80

Val Asp Cys Ser Val Ser Lys Cys Ser Lys Leu Val Gly Gly Gly Glu
85 90 95

35 Ser Asn Pro Met Asn Tyr Asn Ser Tyr Met Asp Glu Lys Asn Gly Pro
100 105 110

40 Pro Pro Pro Asn Met Thr Thr Asn Glu Arg Arg Val Ile Val Pro Ala
115 120 125

45 Asp Pro Thr Leu Trp Thr Gln Glu His Val Arg Gln Trp Leu Glu Trp
130 135 140

Ala Ile Lys Glu Tyr Ser Leu Met Glu Ile Asp Thr Ser Phe Phe Gln
145 150 155 160

50 Asn Met Asp Gly Lys Glu Leu Cys Lys Met Asn Lys Glu Asp Phe Leu
165 170 175

55 Arg Ala Thr Thr Leu Tyr Asn Thr Glu Val Leu Leu Ser His Leu Ser

	180	185	190
5	Tyr Leu Arg Glu Ser Ser Leu Leu Ala Tyr Asn Thr Thr Ser His Thr		
	195	200	205
10	Asp Gln Ser Ser Arg Leu Ser Val Lys Glu Asp Pro Ser Tyr Asp Ser		
	210	215	220
	Val Arg Arg Gly Ala Trp Gly Asn Asn Met Asn Ser Gly Leu Asn Lys		
15	225	230	235
	Ser Pro Pro Leu Gly Gly Ala Gln Thr Ile Ser Lys Asn Thr Glu Gln		240
	245	250	255
20	Arg Pro Gln Pro Asp Pro Tyr Gln Ile Leu Gly Pro Thr Ser Ser Arg		
	260	265	270
25	Leu Ala Asn Pro Gly Ser Gly Gln Ile Gln Leu Trp Gln Phe Leu Leu		
	275	280	285
	Glu Leu Leu Ser Asp Ser Ala Asn Ala Ser Cys Ile Thr Trp Glu Gly		
30	290	295	300
	Thr Asn Gly Glu Phe Lys Met Thr Asp Pro Asp Glu Val Ala Arg Arg		
35	305	310	315
	Trp Gly Glu Arg Lys Ser Lys Pro Asn Met Asn Tyr Asp Lys Leu Ser		320
	325	330	335
40	Arg Ala Leu Arg Tyr Tyr Tyr Asp Lys Asn Ile Met Thr Lys Val His		
	340	345	350
45	Gly Lys Arg Tyr Ala Tyr Lys Phe Asp Phe His Gly Ile Ala Gln Ala		
	355	360	365
50	Leu Gln Pro His Pro Thr Glu Ser Ser Met Tyr Lys Tyr Pro Ser Asp		
	370	375	380
	Ile Ser Tyr Met Pro Ser Gln His Ala His Gln Gln Lys Val Asn Phe		
55	385	390	395
			400

Val Pro Pro His Pro Ser Ser Met Pro Val Thr Ser Ser Ser Phe Phe
 5 405 410 415
 Gly Ala Ala Ser Gln Tyr Trp Thr Ser Thr Gly Gly Ile Tyr Pro Asn
 10 420 425 430
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 15 435 440 445
 Ser Tyr Tyr
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 35 <400> 85
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 45 Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val
 20 25 30
 cct tct gga gag gag cag aga tac acg tgc cat gtg cag cat gag ggg 145
 50 Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly
 35 40 45
 55 cta ccc gag ccc gtc acc ctg aga tgg aag ccg gct tcc cag ccc acc 193

Leu Pro Glu Pro Val Thr Leu Arg Trp Lys Pro Ala Ser Gln Pro Thr
 5 50 55 60
 atc ccc atc gtg ggc atc att gct ggc ctg gtt ctc ctt gga tct gtg 241
 10 Ile Pro Ile Val Gly Ile Ile Ala Gly Leu Val Leu Leu Gly Ser Val
 65 70 75 80
 gtc tct gga gct gtg gtt gct gct gtg ata tgg agg aag aag agc tca 289
 15 Val Ser Gly Ala Val Val Ala Ala Val Ile Trp Arg Lys Lys Ser Ser
 85 90 95
 20 ggt gga aaa gga ggg agc tac tct aag gct gag tgg agc gac agt gcc 337
 Gly Gly Lys Gly Gly Ser Tyr Ser Lys Ala Glu Trp Ser Asp Ser Ala
 100 105 110
 25 cag ggg tct gag tct cac agc ttt taaagcccta gacagctgcc ttgtgtgcca 391
 Gln Gly Ser Glu Ser His Ser Leu
 30 115 120
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 tgtgtcttag gggactctgg ctctctttt tgcaagggcc tctgaatctg tctgtgtccc 511
 35 tgltagcaca atgtgaggag gtagagaaac agtccacctc tgtgtctacc atgacccccct 571
 tctcacact gacctgtgtt ccttccctgt tctcttttct attaaaaata agaaccctggg 631
 40 cagagtgagg cagctcatgc ctgtaatccc agcacctagg gaggccgagg agggcagatc 691
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<210> 86

<211> 120

<212> PRT

<213> Homo sapiens

<400> 86

Gln Gln Asp Gly Glu Gly His Thr Gln Asp Thr Glu Leu Val Glu Thr

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Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly

35 40 45

Leu Pro Glu Pro Val Thr Leu Arg Trp Lys Pro Ala Ser Gln Pro Thr

50 55 60

Ile Pro Ile Val Gly Ile Ile Ala Gly Leu Val Leu Leu Gly Ser Val

65 70 75 80
 5 Val Ser Gly Ala Val Val Ala Ala Val Ile Trp Arg Lys Lys Ser Ser
 85 90 95
 10 Gly Gly Lys Gly Gly Ser Tyr Ser Lys Ala Glu Trp Ser Asp Ser Ala
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 15 Gln Gly Ser Glu Ser His Ser Leu
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 50 tcc tac gtg gcc cac ctg gcc tca gac ttc ggg glg agg glg ttt cag 207
 Ser Tyr Val Ala His Leu Ala Ser Asp Phe Gly Val Arg Val Phe Gln
 30 35 40
 55 cag glg gcg cag gcc tcc aag gac cgc aac glg gtt ttc tca ccc tat 255

Gln Val Ala Gln Ala Ser Lys Asp Arg Asn Val Val Phe Ser Pro Tyr
 45 50 55 60
 5 ggg gtg gcc tcg gtg ttg gcc alg ctc cag ctg aca aca gga gga gaa 303
 Gly Val Ala Ser Val Leu Ala Met Leu Gln Leu Thr Thr Gly Gly Glu
 10 65 70 75
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 15 Thr Gln Gln Gln Ile Gln Ala Ala Met Gly Phe Lys Ile Asp Asp Lys
 80 85 90
 ggc alg gcc ccc gcc ctc cgg cat ctg tac aag gag ctc atg ggg cca 399
 20 Gly Met Ala Pro Ala Leu Arg His Leu Tyr Lys Glu Leu Met Gly Pro
 95 100 105
 25 tgg aac aag gat gag atc agc acc aca gac gcg atc ttc gtc cag cgg 447
 Trp Asn Lys Asp Glu Ile Ser Thr Thr Asp Ala Ile Phe Val Gln Arg
 110 115 120
 30 gat ctg aag ctg gtc cag ggc ttc atg ccc cac ttc ttc agg ctg ttc 495
 Asp Leu Lys Leu Val Gln Gly Phe Met Pro His Phe Phe Arg Leu Phe
 35 125 130 135 140
 cgg agc acg gtc aag caa gtg gac ttt tca gag gtg gag aga gcc aga 543
 40 Arg Ser Thr Val Lys Gln Val Asp Phe Ser Glu Val Glu Arg Ala Arg
 145 150 155
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 45 Phe Ile Ile Asn Asp Trp Val Lys Thr His Thr Lys Gly Met Ile Ser
 160 165 170
 50 aac ttg ctt ggg aaa gga gcc gtg gac cag ctg aca cgg ctg gtg ctg 639
 Asn Leu Leu Gly Lys Gly Ala Val Asp Gln Leu Thr Arg Leu Val Leu
 175 180 185
 55 gtg aat gcc ctc tac ttc aac ggc cag tgg aag act ccc ttc ccc gac 687

EP 1 225 224 A1

Val Asn Ala Leu Tyr Phe Asn Gly Gln Trp Lys Thr Pro Phe Pro Asp
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Ser Ser Thr His Arg Arg Leu Phe His Lys Ser Asp Gly Ser Thr Val
10 205 210 215 220
tct gtc ccc atg atg gct cag acc aac aag ttc aac tat act gag ttc 783
15 Ser Val Pro Met Met Ala Gln Thr Asn Lys Phe Asn Tyr Thr Glu Phe
225 230 235
20 acc acg ccc gat ggc cat tac tac gac atc ctg gaa ctg ccc tac cac 831
Thr Thr Pro Asp Gly His Tyr Tyr Asp Ile Leu Glu Leu Pro Tyr His
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25 ggc gac acc ctc agc atg ttc att gct gcc cct tat gaa aaa gag gtg 879
Gly Asp Thr Leu Ser Met Phe Ile Ala Ala Pro Tyr Glu Lys Glu Val
30 255 260 265
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35 Pro Leu Ser Ala Leu Thr Asn Ile Leu Ser Ala Gln Leu Ile Ser His
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285 290 295 300
45 ttc tcc ctg gag act gaa gtc gac ctc agg aag ccc cta gag aac ctg 1023
Phe Ser Leu Glu Thr Glu Val Asp Leu Arg Lys Pro Leu Glu Asn Leu
305 310 315
50 gga atg acc gac atg ttc aga cag ttt cag gct gac ttc acg agt ctt 1071
Gly Met Thr Asp Met Phe Arg Gln Phe Gln Ala Asp Phe Thr Ser Leu
55 320 325 330

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 5 335 340 345
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 350 355 360
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 15 Ile Val Ser Ala Arg Met Ala Pro Glu Glu Ile Ile Met Asp Arg Pro
 365 370 375 380
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 385 390 395
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55 20 25 30
 Ala Ser Lys Asp Arg Asn Val Val Phe Ser Pro Tyr Gly Val Ala Ser

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	210	215	220													
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	225	230	235	240												
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	Thr Glu Val Asp Leu Arg Lys Pro Leu Glu Asn Leu Gly Met Thr Asp		
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	Met Phe Arg Gln Phe Gln Ala Asp Phe Thr Ser Leu Ser Asp Gln Glu		
20	305	310	315
	Pro Leu His Val Ala Gln Ala Leu Gln Lys Val Lys Ile Glu Val Asn		320
	325	330	335
25	Glu Ser Gly Thr Val Ala Ser Ser Ser Thr Ala Val Ile Val Ser Ala		
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30	Arg Met Ala Pro Glu Glu Ile Ile Met Asp Arg Pro Phe Leu Phe Val		
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 55 ctg gct cgg aag aac cga gag gag cta gac aag tac tgg tct cag cag 873

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 10 275 280 285 290
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 30 aac ggg atc ctg ctg cac ctt gag tca gag ctg gca cag acc cgg gca 1113
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 35 340 345 350
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 40 Glu Gly Gln Arg Gln Ala Gln Glu Tyr Glu Ala Leu Leu Asn Ile Lys
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 375 380 385
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 5 405 410 415
 gtg tct gag acc aat gac acc aaa gtt ctg agg cat taagccagca 1351
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 40 35 40 45
 Ser Arg Ser Thr Ser Phe Arg Gly Gly Met Gly Ser Gly Gly Leu Ala
 45 50 55 60
 Thr Gly Ile Ala Gly Gly Leu Ala Gly Met Gly Gly Ile Gln Asn Glu
 65 70 75 80
 Lys Glu Thr Met Gln Ser Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
 50 85 90 95
 Arg Val Arg Ser Leu Glu Thr Glu Asn Arg Arg Leu Glu Ser Lys Ile
 55 100 105 110

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	Val Asp Asn Ala Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu Ala			
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	Ala Asp Asp Phe Arg Val Lys Tyr Glu Thr Glu Leu Ala Met Arg Gln			
	165	170	175	
20	Ser Val Glu Asn Asp Ile His Gly Leu Arg Lys Val Ile Asp Asp Thr			
	180	185	190	
25	Asn Ile Thr Arg Leu Gln Leu Glu Thr Glu Ile Glu Ala Leu Lys Glu			
	195	200	205	
	Glu Leu Leu Phe Met Lys Lys Asn His Glu Glu Glu Val Lys Gly Leu			
30	210	215	220	
	Gln Ala Gln Ile Ala Ser Ser Gly Leu Thr Val Glu Val Asp Ala Pro			
35	225	230	235	240
	Lys Ser Gln Asp Leu Ala Lys Ile Met Ala Asp Ile Arg Ala Gln Tyr			
	245	250	255	
40	Asp Glu Leu Ala Arg Lys Asn Arg Glu Glu Leu Asp Lys Tyr Trp Ser			
	260	265	270	
45	Gln Gln Ile Glu Glu Ser Thr Thr Val Val Thr Thr Gln Ser Ala Glu			
	275	280	285	
	Val Gly Ala Ala Glu Thr Thr Leu Thr Glu Leu Arg Arg Thr Val Gln			
50	290	295	300	
	Ser Leu Glu Ile Asp Leu Asp Ser Met Arg Asn Leu Lys Ala Ser Leu			
55	305	310	315	320

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 5 Gln Leu Asn Gly Ile Leu Leu His Leu Glu Ser Glu Leu Ala Gln Thr
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 10 Arg Ala Glu Gly Gln Arg Gln Ala Gln Glu Tyr Glu Ala Leu Leu Asn
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 15 Ile Lys Val Lys Leu Glu Ala Glu Ile Ala Thr Tyr Arg Arg Leu Leu
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 20 Glu Asp Gly Glu Asp Phe Asn Leu Gly Asp Ala Leu Asp Ser Ser Asn
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 ggtgccctgaa tgggaacccc ccgaagcgcc tgaaaaggag agacaggagg atg atg 176
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 5 Ser Gln Leu Glu Leu Leu Ser Gly Gly Glu Met Leu Cys Gly Gly Phe
 5 10 15
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 10 Tyr Pro Arg Leu Ser Cys Cys Leu Arg Ser Asp Ser Pro Gly Leu Gly
 20 25 30
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 15 Arg Leu Glu Asn Lys Ile Phe Ser Val Thr Asn Asn Thr Glu Cys Gly
 20 35 40 45 50
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 55 60 65
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 30 Ser Leu Phe His Ser Pro Glu Arg Glu Val Leu Glu Arg Asp Leu Val
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 85 90 95
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 40 Arg Gly His Ile Pro Gly Phe Leu Gln Thr Thr Ala Asp Glu Phe Cys
 45 100 105 110
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 50 Phe Tyr Tyr Ala Arg Lys Asp Gly Gly Leu Cys Phe Pro Asp Phe Pro
 115 120 125 130
 aga aaa caa gtc aga gga cca gca tct aac tac ttg gac cag atg gaa 608
 55 Arg Lys Gln Val Arg Gly Pro Ala Ser Asn Tyr Leu Asp Gln Met Glu

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	Glu Tyr Asp Lys Val Glu Glu Ile Ser Arg Lys His Lys His Asn Cys			
	150	155	160	
10	ttc tgt att cag gag gtt gtg agt ggg ctg cgg cag ccc gtt ggt gcc			704
	Phe Cys Ile Gln Glu Val Val Ser Gly Leu Arg Gln Pro Val Gly Ala			
15	165	170	175	
	ctg cat agt ggg gat ggc tgc caa cgt ctc ttc att ctg gaa aaa gaa			752
20	Leu His Ser Gly Asp Gly Ser Gln Arg Leu Phe Ile Leu Glu Lys Glu			
	180	185	190	
25	ggt tat gtg aag ata ctt acc cct gaa gga gaa att ttc aag gag cct			800
	Gly Tyr Val Lys Ile Leu Thr Pro Glu Gly Glu Ile Phe Lys Glu Pro			
	195	200	205	210
30	tat ttg gac att cac aaa ctt gtt caa agt gga ata aag gtt ggc ttt			848
	Tyr Leu Asp Ile His Lys Leu Val Gln Ser Gly Ile Lys Val Gly Phe			
	215	220	225	
35	tta aat ttt att tat ttt tgt gct ggc tac gtt aat ttt att tta gtg			896
	Leu Asn Phe Ile Tyr Phe Cys Ala Gly Tyr Val Asn Phe Ile Leu Val			
40	230	235	240	
	tta cct tcc tca ctg aag gla ttt ctt tgt aat aaa aga aag aat ctt			944
45	Leu Pro Ser Ser Leu Lys Val Phe Leu Cys Asn Lys Arg Lys Asn Leu			
	245	250	255	
50	gca gga gaa aat aag ggg gca aca taagaacaa taattatggc accigaattia			998
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35 40 45

Cys Gly Lys Leu Leu Glu Glu Ile Lys Cys Ala Leu Cys Ser Pro His

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Ser Gln Ser Leu Phe His Ser Pro Glu Arg Glu Val Leu Glu Arg Asp

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Leu Val Leu Pro Leu Leu Cys Lys Asp Tyr Cys Lys Glu Phe Phe Tyr

85 90 95

Thr Cys Arg Gly His Ile Pro Gly Phe Leu Gln Thr Thr Ala Asp Glu

100 105 110

Phe Cys Phe Tyr Tyr Ala Arg Lys Asp Gly Gly Leu Cys Phe Pro Asp

115 120 125

Phe Pro Arg Lys Gln Val Arg Gly Pro Ala Ser Asn Tyr Leu Asp Gln

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Met Glu Glu Tyr Asp Lys Val Glu Glu Ile Ser Arg Lys His Lys His

145 150 155 160

Asn Cys Phe Cys Ile Gln Glu Val Val Ser Gly Leu Arg Gln Pro Val

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 10 195 200 205
 Glu Pro Tyr Leu Asp Ile His Lys Leu Val Gln Ser Gly Ile Lys Val
 15 210 215 220
 Gly Phe Leu Asn Phe Ile Tyr Phe Cys Ala Gly Tyr Val Asn Phe Ile
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Phe Leu Ile Ser Ala Ala Leu Cys Glu Gly Ala Val Leu Pro Arg Ser
 5 15 20 25
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 Ala Lys Glu Leu Arg Cys Gln Cys Ile Lys Thr Tyr Ser Lys Pro Phe
 10 30 35 40
 cac ccc aaa ttt atc aaa gaa ctg aga glg att gag agt gga cca cac 254
 His Pro Lys Phe Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His
 15 45 50 55 60
 tgc gcc aac aca gaa att att gta aag ctt tct gat gga aga gag ctc 302
 Cys Ala Asn Thr Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu
 20 65 70 75
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 Cys Leu Asp Pro Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe
 25 80 85 90
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 Leu Lys Arg Ala Glu Asn Ser
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<211> 99

<212> PRT

<213> Homo sapiens

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 20 25 30
 Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr
 35 40 45
 Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro
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	Cys Cys Cys Cys Pro Arg Val Ala Gly Val Pro Gly Glu Ala Glu Gln			
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40	Pro Ala Pro Glu Leu Val Glu Val Glu Val Gly Ser Thr Ala Leu Leu			
	35	40	45	
	aag tgc ggc ctc tcc cag tcc caa ggc aac ctc agc cat gtc gac tgg 193			
45	Lys Cys Gly Leu Ser Gln Ser Gln Gly Asn Leu Ser His Val Asp Trp			
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50	ttt tct gtc cac aag gag aag cgg acg ctc atc ttc cgt gtg cgc cag 241			
	Phe Ser Val His Lys Glu Lys Arg Thr Leu Ile Phe Arg Val Arg Gln			
55	65	70	75	
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 5 80 85 90
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 10 Gln Asp Arg Gly Ala Thr Leu Ala Leu Thr Gln Val Thr Pro Gln Asp
 95 100 105 110
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 15 Glu Arg Ile Phe Leu Cys Gln Gly Lys Arg Pro Arg Ser Gln Glu Tyr
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640

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25	gag cct gaa gtt ttt aag gaa atg atg tgc ttc att tac acg ggg aag	943		
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	Ala Pro Asn Leu Asp Lys Met Ala Asp Asp Leu Leu Ala Ala Ala Asp			
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Gly Glu Val Ile Lys Ser Ser Thr Phe Ser Ser Gly Ala Asn Asp Lys
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 5 Leu Lys Trp Cys Leu Arg Val Asn Pro Lys Gly Leu Asp Glu Glu Ser
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	Glu	Trp	Thr	Ser	Cys	Ser	Thr	Ser	Cys	Gly	Asn	Gly	Ile	Gln	Gln	Arg	
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	Gly	Arg	Ser	Cys	Asp	Ser	Leu	Asn	Asn	Arg	Cys	Glu	Gly	Ser	Ser	Val	
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EP 1 225 224 A1

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 Pro Lys His Leu Asn Asp Asp Val Val Lys Ile Asp Phe Glu Asp Val
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Ser Leu Met Phe Leu Leu Ser Tyr Leu Phe Gly Phe Tyr Lys Arg Phe

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Glu Ser Trp Arg Val Leu Asp Ser Leu Tyr His Gly Thr Thr Gly Ile

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Leu Tyr Met Ser Ala Ala Val Leu Gln Val His Ala Thr Ile Val Ser

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Met Ala Ala Pro Met Thr Pro Ala

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Ala Arg Pro Glu Asp Tyr Glu Ala Ala Leu Asn Ala Ala Leu Ala Asp

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Lys Asn Ile Gly Glu Asn Glu Gly Gly Ile Asp Lys Phe Ser Arg Gly

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Tyr Glu Ser Phe Gly Val His Arg Cys Ala Asp Gly Gly Leu Tyr Ser

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	Cys Ile Ala Tyr Ala Glu Ser His Asp Gln Ala Leu Val Gly Asp Lys			
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55	gic ctg act cct ttt act cca gtt att gat cgt gga ata cag ctt cat	1650		
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	Asn Phe Met Gly Asn Glu Phe Gly His Pro Glu Trp Leu Asp Phe Pro				
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Tyr Lys Gln Phe Ser Gln Ile Leu Lys Asn Ile Gly Glu Asn Glu Gly

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Gly Ile Asp Lys Phe Ser Arg Gly Tyr Glu Ser Phe Gly Val His Arg

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Cys Ala Asp Gly Gly Leu Tyr Ser Lys Glu Trp Ala Pro Gly Ala Glu

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Gly Val Phe Leu Thr Gly Asp Phe Asn Gly Trp Asn Pro Phe Ser Tyr

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35

Pro Tyr Lys Lys Leu Asp Tyr Gly Lys Trp Glu Leu Tyr Ile Pro Pro

115 120 125

Lys Gln Asn Lys Ser Val Leu Val Pro His Gly Ser Lys Leu Lys Val

40

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Val Ile Thr Ser Lys Ser Gly Glu Ile Leu Tyr Arg Ile Ser Pro Trp

45

145 150 155 160

Ala Lys Tyr Val Val Arg Glu Gly Asp Asn Val Asn Tyr Asp Trp Ile

165 170 175

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His Trp Asp Pro Glu His Ser Tyr Glu Phe Lys His Ser Arg Pro Lys

180 185 190

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Lys Pro Arg Ser Leu Arg Ile Tyr Glu Ser His Val Gly Ile Ser Ser

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	Leu Trp Asp Ser Arg Leu Phe Ala Tyr Ser Ser Trp Glu Val Leu Arg		
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	Gly Leu Gly Gly Glu Gly Tyr Leu Asn Phe Met Gly Asn Glu Phe Gly		
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10	Arg Asp Asp Val Ala Leu Lys Asn Phe Ala Lys Tyr Phe Leu His Gln	
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	Ser His Glu Glu Arg Glu His Ala Glu Lys Leu Met Lys Leu Gln Asn	
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40	gac aaa aat gac ccc cat ttg tgt gac ttc att gag aca cat tac ctg	494
	Asp Lys Asn Asp Pro His Leu Cys Asp Phe Ile Glu Thr His Tyr Leu	
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 35 35 40 45
 Leu Lys Asn Phe Ala Lys Tyr Phe Leu His Gln Ser His Glu Glu Arg
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	glg ctc ctc gtg rgg cag tac agc acg ggc aag acc acc ttc atc cga	483		
	Val Leu Leu Val Xaa Gln Tyr Ser Thr Gly Lys Thr Thr Phe Ile Arg			
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30	acc acc gac tcc ttc atc gcc gtc atg cac ggc ccc act gag ggc glg	579		
	Thr Thr Asp Ser Phe Ile Ala Val Met His Gly Pro Thr Glu Gly Val			
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35	gtg ccg ggc aac gcg ctc gtg gtg gac ccg cgg cgc ccc ttc cgc aag	627		
	Val Pro Gly Asn Ala Leu Val Val Asp Pro Arg Arg Pro Phe Arg Lys			
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	ctc aac gcg ttt ggc aac gct ttc ctc aac agg ttc atg tgt gcc cag	675		
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	Phe Asp Ala His Lys Leu Asp Ile Ser Asp Glu Phe Ser Glu Val Ile			
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	205	210	215	220
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25	Ala Asp Gln Ile Glu Thr Gln Gln Leu Met Arg Val Tyr Gly Ala Leu			
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30	atg tgg tcc ctg ggc aag atc atc aac acc ccc gag glg gtc agg gtc			1011
	Met Trp Ser Leu Gly Lys Ile Ile Asn Thr Pro Glu Val Val Arg Val			
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	Tyr Ile Gly Ser Phe Trp Ser His Pro Leu Leu Ile Pro Asp Asn Arg			
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45	Ala Phe Asp Gly Thr Met Asn Gly Pro Phe Gly His Gly Tyr Gly Glu	
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50	ggg gcc ggc gag ggc atc cac gac gtg gag tgg gtg gtg ggc aag gac	1587
	Gly Ala Gly Glu Gly Ile His Asp Val Glu Trp Val Val Gly Lys Asp	
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10	Xaa Leu Glu Asp Ala Asp Phe Asp Asn Lys Pro Met Val Leu Leu Val		
	50	55	60
	Xaa Gln Tyr Ser Thr Gly Lys Thr Thr Phe Ile Arg His Leu Ile Glu		
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	Gln Asp Phe Pro Gly Met Arg Ile Gly Pro Glu Pro Thr Thr Asp Ser		80
	85	90	95
20	Phe Ile Ala Val Met His Gly Pro Thr Glu Gly Val Val Pro Gly Asn		
	100	105	110
25	Ala Leu Val Val Asp Pro Arg Arg Pro Phe Arg Lys Leu Asn Ala Phe		
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30	Gly Asn Ala Phe Leu Asn Arg Phe Met Cys Ala Gln Leu Pro Asn Pro		
	130	135	140
	Val Leu Asp Ser Ile Ser Ile Ile Asp Thr Pro Gly Ile Leu Ser Gly		
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	Glu Lys Gln Arg Ile Ser Arg Gly Tyr Asp Phe Ala Ala Val Leu Glu		160
	165	170	175
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50	Asn His Glu Asp Lys Ile Arg Val Val Leu Asn Lys Ala Asp Gln Ile		
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			240

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	Phe Trp Ser His Pro Leu Leu Ile Pro Asp Asn Arg Lys Leu Phe Glu		
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	Glu Ser Leu Met Pro Ser Gln Val Val Lys Gly Gly Ala Phe Asp Gly		
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	Thr Met Asn Gly Pro Phe Gly His Gly Tyr Gly Glu Gly Ala Gly Glu		
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	Gly Ile His Asp Val Glu Trp Val Val Gly Lys Asp Lys Pro Thr Tyr		
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25	Val Ile Ala Leu Gln Tyr Pro Val Tyr Trp Asp His Leu Glu Phe Cys			
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Leu Pro Pro Val Ser Gly Thr Ala Asp Val Phe Phe Arg Gln Ile Leu

50 55 60

Ala Leu Thr Gly Trp Gly Tyr Arg Val Ile Ala Leu Gln Tyr Pro Val

65 70 75 80

Tyr Trp Asp His Leu Glu Phe Cys Asp Gly Phe Arg Lys Leu Leu Asp

85 90 95

His Leu Gln Leu Asp Lys Val His Leu Phe Gly Ala Ser Leu Gly Gly

100 105 110

Phe Leu Ala Gln Lys Phe Ala Glu Tyr Thr His Lys Ser Pro Arg Val

115 120 125

His Ser Leu Ile Leu Cys Asn Ser Phe Ser Asp Thr Ser Ile Phe Asn

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Gln Thr Trp Thr Ala Asn Ser Phe Trp Leu Met Pro Ala Phe Met Leu

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Lys Lys Ile Val Leu Gly Asn Phe Ser Ser Gly Pro Val Asp Pro Met

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 35 kcw tty kkc tcc aaa acg tgg att gag glc lca ggt tcc tct scc aaa 96
 Xaa Xaa Xaa Ser Lys Thr Trp Ile Glu Val Ser Gly Ser Ser Xaa Lys
 40 20 25 30
 gat gyt kca aag cag ctg aag gag cag cag atg gtg atg aga ggc cac 144
 45 Asp Xaa Xaa Lys Gln Leu Lys Glu Gln Gln Met Val Met Arg Gly His
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 50 cga gag acc tcc atg gtc cal gaa ctc aac cgg lac atc ccc aca gcc 192
 Arg Glu Thr Ser Met Val His Glu Leu Asn Arg Tyr Ile Pro Thr Ala
 50 55 60
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Ala Ala Phe Gly Gly Leu Cys Ile Gly Ala Leu Ser Val Leu Ala Asp
5 65 70 75 80
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Phe Leu Gly Ala Ile Gly Ser Gly Thr Gly Ile Leu Leu Ala Val Thr
10 85 90 95
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ggc agc atg ggg gcc ctg ctc ttc tgagcccgtc tcccgacag gttgaggaag 390
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 35 40 45
 50 Arg Glu Thr Ser Met Val His Glu Leu Asn Arg Tyr Ile Pro Thr Ala
 50 55 60
 55 Ala Ala Phe Gly Gly Leu Cys Ile Gly Ala Leu Ser Val Leu Ala Asp

65 70 75 80
 5 Phe Leu Gly Ala Ile Gly Ser Gly Thr Gly Ile Leu Leu Ala Val Thr
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 45
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gggc

364

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agc tgg gct aac ctt tcc cga act tgt ttc ccg gag gca agg tgc tgc 100

Ser Trp Ala Asn Leu Ser Arg Thr Cys Phe Pro Glu Ala Arg Cys Ser

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15

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gtg acc cag cgc atc tta acc ttg ggt clc cta ggc tgc agg cta ggg 148

Val Thr Gln Arg Ile Leu Thr Leu Gly Leu Leu Gly Ser Arg Leu Gly

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30

35

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cat tac gtt tgc tgg aac caa agc agc caa ttg cat agc aag tat ttt 196

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His Tyr Val Ser Trp Asn Gln Ser Ser Gln Leu His Ser Lys Tyr Phe

45

50

55

55

cct gca ttc caa tta aat gct taagaaaaag cagcatccta laaaattgtg 247

Pro Ala Phe Gln Leu Asn Ala

60

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cagctgttgg ctgaccagaa taaactccct gctgagtica agcttgaat ggaatggag 487

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caaatgatgt tgtttccatt agagcaggtg ctacacagcat tctgatlggc ctgagcagac 547

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852

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15

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55

20

25

30

Leu Gly Leu Leu Gly Ser Arg Leu Gly His Tyr Val Ser Trp Asn Gln

5

35

40

45

Ser Ser Gln Leu His Ser Lys Tyr Phe Pro Ala Phe Gln Leu Asn Ala

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55

Met Leu Lys Cys

5 gtg gtg gtg ggg gac ggt gcc gtg ggg aaa acc tgc ctg ctg atg agc 583
 Val Val Val Gly Asp Gly Ala Val Gly Lys Thr Cys Leu Leu Met Ser
 5 10 15 20
 10 tac gcc aac gac gcc ttc cca gag gaa tac gtg ccc act gtg ttt gac 631
 Tyr Ala Asn Asp Ala Phe Pro Glu Glu Tyr Val Pro Thr Val Phe Asp
 25 30 35
 15 cac tat gca gtt act gtg act gtg gga ggc aag caa cac ttg ctc gga 679
 His Tyr Ala Val Thr Val Thr Val Gly Gly Lys Gln His Leu Leu Gly
 40 45 50
 20 ctg tat gac acc gcg gga cag gag gac tac aac cag ctg agg cca ctc 727
 Leu Tyr Asp Thr Ala Gly Gln Glu Asp Tyr Asn Gln Leu Arg Pro Leu
 55 60 65
 25 tcc tac ccc aac acg gat gtg ttt ttg atc tgc ttc tct gtc gta aac 775
 Ser Tyr Pro Asn Thr Asp Val Phe Leu Ile Cys Phe Ser Val Val Asn
 70 75 80
 30 cct gcc tct tac cac aat gtc cag gag gaa tgg gtc ccc gag ctc aag 823
 Pro Ala Ser Tyr His Asn Val Gln Glu Glu Trp Val Pro Glu Leu Lys
 85 90 95 100
 35 gac tgc atg cct cac gtg cct tat gtc ctc ata ggg acc cag att gat 871
 Asp Cys Met Pro His Val Pro Tyr Val Leu Ile Gly Thr Gln Ile Asp
 105 110 115
 40 ctc cgt gat gac cca aaa acc ttg gcc cgt ttg ctg tat atg aaa gag 919
 Leu Arg Asp Asp Pro Lys Thr Leu Ala Arg Leu Leu Tyr Met Lys Glu
 120 125 130
 45 aaa cct ctc act tac gag cat ggt gtg aag ctc gca aaa gcg atc gga 967
 Lys Pro Leu Thr Tyr Glu His Gly Val Lys Leu Ala Lys Ala Ile Gly
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 55

EP 1 225 224 A1

135 140 145

5 gca cag tgc tac ttg gaa tgt tca gct ctg act cag aaa ggt ctc aaa 1015
Ala Gln Cys Tyr Leu Glu Cys Ser Ala Leu Thr Gln Lys Gly Leu Lys

10 150 155 160
gcg gtt ttt gat gaa gca atc ctc acc att ttc cac ccc aag aaa aag 1063
Ala Val Phe Asp Glu Ala Ile Leu Thr Ile Phe His Pro Lys Lys Lys

15 165 170 175 180
aag aaa cgc tgt tct gag ggt cac agc tgc tgt tca att atc 1105
Lys Lys Arg Cys Ser Glu Gly His Ser Cys Cys Ser Ile Ile

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Thr Val Phe Asp His Tyr Ala Val Thr Val Thr Val Gly Gly Lys Gln

50 35 40 45
His Leu Leu Gly Leu Tyr Asp Thr Ala Gly Gln Glu Asp Tyr Asn Gln

55 50 55 60
Leu Arg Pro Leu Ser Tyr Pro Asn Thr Asp Val Phe Leu Ile Cys Phe

65 70 75 80

5 Ser Val Val Asn Pro Ala Ser Tyr His Asn Val Gln Glu Glu Trp Val
 85 90 95
 Pro Glu Leu Lys Asp Cys Met Pro His Val Pro Tyr Val Leu Ile Gly
 10 100 105 110
 Thr Gln Ile Asp Leu Arg Asp Asp Pro Lys Thr Leu Ala Arg Leu Leu
 115 120 125
 15 Tyr Met Lys Glu Lys Pro Leu Thr Tyr Glu His Gly Val Lys Leu Ala
 130 135 140
 20 Lys Ala Ile Gly Ala Gln Cys Tyr Leu Glu Cys Ser Ala Leu Thr Gln
 145 150 155 160
 25 Lys Gly Leu Lys Ala Val Phe Asp Glu Ala Ile Leu Thr Ile Phe His
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acc glg tat gcc ctg gcg glc atc lcg acg cca gac cag acc aaa gtc 97

55 Thr Val Tyr Ala Leu Ala Val Ile Ser Thr Pro Asp Gln Thr Lys Val

20 25 30
 5 ttc agt gca tcc tac gac cgg tcc ctc agg gtc tgg agt atg gac aac 145
 Phe Ser Ala Ser Tyr Asp Arg Ser Leu Arg Val Trp Ser Met Asp Asn
 35 40 45
 10 atg atc tgc acg cag acc ctc ctc cgt cac cag ggc agt gtc acc ggc 193
 Met Ile Cys Thr Gln Thr Leu Leu Arg His Gln Gly Ser Val Thr Ala
 50 55 60
 15 ctc gct gtg tcc cgg ggc cga ctc ttc tca ggg gct gtg gat agc act 241
 Leu Ala Val Ser Arg Gly Arg Leu Phe Ser Gly Ala Val Asp Ser Thr
 20 65 70 75 80
 gtg aag gtt tgg act tgc taacaggatc caggccaggc tgtggtttcc 289
 25 Val Lys Val Trp Thr Cys
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Thr Val Tyr Ala Leu Ala Val Ile Ser Thr Pro Asp Gln Thr Lys Val

20

25

30

55

Phe Ser Ala Ser Tyr Asp Arg Ser Leu Arg Val Trp Ser Met Asp Asn

35

40

45

Met Ile Cys Thr Gln Thr Leu Leu Arg His Gln Gly Ser Val Thr Ala
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gccaaacttg gttaagact aggtcttccc tggcaagttc cggaaga atg gac tta 176

Met Asp Leu

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ctg act ttt atc aac tct tct cac tgc caa ggc caa cag cat ctg agg 224

Leu Thr Phe Ile Asn Ser Ser His Cys Gln Gly Gln Gln His Leu Arg

5

10

15

tat agc ttt ttg gga gta cct gct ttc ttg cct cct gga gga tat ttt 272

Tyr Ser Phe Leu Gly Val Pro Ala Phe Leu Pro Pro Gly Gly Tyr Phe

20

25

30

35

ctg tcc tgg ggc ttc atg gcc cct ctc ttc cct gtt aca cat tgc tgt 320

Leu Ser Trp Gly Phe Met Ala Pro Leu Phe Pro Val Thr His Cys Cys

40

45

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gct tca gag cct ttg cag ctg cra cct agt tgaatccaca taggsttctt 370

Ala Ser Glu Pro Leu Gln Leu Xaa Pro Ser

55

60

tccacacggt gggaaggatc ttgctgcttt cactcacagg accagggagt tyttcaatca 430

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<212> PRT

<213> Homo sapiens

<220>

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Gly Tyr Phe Leu Ser Trp Gly Phe Met Ala Pro Leu Phe Pro Val Thr

35 40 45

His Cys Cys Ala Ser Glu Pro Leu Gln Leu Xaa Pro Ser

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 30 tta cag agc aga aga cag atg ccc aaa cag gag aag gca ctt gcc cac 825
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30

Gln Arg Ala Ser Leu Pro Leu Pro Glu Pro Gly Ser Pro Ile Lys Pro

35

40

45

Thr Ser Cys Leu Lys Ser Ile Ser Gly Ser Leu Thr Ser Asn Arg Pro

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5

10

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 15 ttaactccga ccagaacctc tcttctcttg gcactcccca cccatagacc ttcatatcat 780
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 35 gggigaactg aatgtatttc ttacccaaat ctgaltgta acaattaaaa agaagaatg 180
 40 acaigcaagt aggccttagc agaaaaatgc aggcctggca tgagtcaigt tgitaccctc 240
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Met

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 Ser Tyr Pro Phe Lys Gln Leu Leu Ala Ser Phe Lys Pro Lys Ile Tyr

aca cat agt tct gta ala aaa ctg ttt gac ttc tca agt aac atg act 633
 Thr His Ser Ser Val Ile Lys Leu Phe Asp Phe Ser Ser Asn Met Thr

tcc tta ttt ctg aac agt act ggt tac ttt caa aat gaa ttt tta ttg 681
 Ser Leu Phe Leu Asn Ser Thr Gly Tyr Phe Gln Asn Glu Phe Leu Leu

aga ttt tcc att aac tat ttt ttt caa aga ctg aaa ttt tgt acc aag 729

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Arg Phe Ser Ile Asn Tyr Phe Phe Gln Arg Leu Lys Phe Cys Thr Lys

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Lys

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 55 ttg ctc act aac tat tcc ttt tta lgg cct ggg gtt aaa ggg agc atg 96

Leu Leu Thr Asn Tyr Ser Phe Leu Trp Pro Gly Val Lys Gly Ser Met
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 Ala His Thr Gly Glu Asn Lys Glu Gly Leu Val Leu Ser Cys Ile Asn
 10 35 40 45
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 Asn Thr Gly Cys Ile Pro Pro Ala Arg Asp Phe Tyr Leu Arg Arg Pro
 15 50 55 60
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 Met Lys His
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 30 twgtaartaa cataatgtcc ttattatttt atatttaagc atctaacata tagagttgtt 421
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20 25 30
 5 Ala His Thr Gly Glu Asn Lys Glu Gly Leu Val Leu Ser Cys Ile Asn
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 Met Ser Leu Ser
 40 1
 agg gac ctc aag gac gac ttt cac agt gac acg gla ctc tcc atc tta 162
 45 Arg Asp Leu Lys Asp Asp Phe His Ser Asp Thr Val Leu Ser Ile Leu
 5 10 15 20
 aat gag cag cgc att cgg ggc att tta tgc gat glc act atc att gig 210
 50 Asn Glu Gln Arg Ile Arg Gly Ile Leu Cys Asp Val Thr Ile Ile Val
 25 30 35
 55 gaa gat acc aaa ttt aaa gcc cat agc aat gtt clg gca gct tca agc 258

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Glu Asp Thr Lys Phe Lys Ala His Ser Asn Val Leu Ala Ala Ser Ser
 5 40 45 50
 ctg tat ttt aaa aat atc ttt tgg agc cat aca atc tgt att tcc agc 306
 Leu Tyr Phe Lys Asn Ile Phe Trp Ser His Thr Ile Cys Ile Ser Ser
 10 55 60 65
 cac gtc ctg gag ctg gac gat ctc aaa gct gaa gtg ttt act gaa ata 354
 His Val Leu Glu Leu Asp Asp Leu Lys Ala Glu Val Phe Thr Glu Ile
 15 70 75 80
 ctt aat tat atc tac agt tcc aca gtc gtt gtc aag aga cag gaa aca 402
 Leu Asn Tyr Ile Tyr Ser Ser Thr Val Val Val Lys Arg Gln Glu Thr
 20 85 90 95 100
 gtc act gat ctc gca gct gca gga aaa aag ctg gga ata tcg ttc ttg 450
 Val Thr Asp Leu Ala Ala Ala Gly Lys Lys Leu Gly Ile Ser Phe Leu
 25 105 110 115
 gaa gac ctt act gat cgc aac ttc tca aat tcc ccg ggt ccc tat gla 498
 Glu Asp Leu Thr Asp Arg Asn Phe Ser Asn Ser Pro Gly Pro Tyr Val
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 10 Thr Ile Ile Val Glu Asp Thr Lys Phe Lys Ala His Ser Asn Val Leu
 35 40 45
 15 Ala Ala Ser Ser Leu Tyr Phe Lys Asn Ile Phe Trp Ser His Thr Ile
 50 55 60
 Cys Ile Ser Ser His Val Leu Glu Leu Asp Asp Leu Lys Ala Glu Val
 65 70 75 80
 20 Phe Thr Glu Ile Leu Asn Tyr Ile Tyr Ser Ser Thr Val Val Val Lys
 85 90 95
 25 Arg Gln Glu Thr Val Thr Asp Leu Ala Ala Ala Gly Lys Lys Leu Gly
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 Met Ile Ser Leu Pro Gly Pro Leu Val Thr Asn
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 Leu Leu Arg Phe Leu Phe Leu Gly Leu Ser Ala Leu Ala Pro Pro Ser
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 Arg Ala Gln Leu Gln Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val
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 25 Glu Gly Gly Glu Val Val Leu Pro Ala Trp Tyr Thr Leu His Gly Glu
 45 50 55
 30 gtg tct tca tcc cag cca tgg gag gtc ccc ttt gtg atg tgg ttc ttc 362
 Val Ser Ser Ser Gln Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe
 60 65 70 75
 35 aaa cag aaa gaa aag gag gat cag gtc ttg tcc tac atc aat ggg gtc 410
 Lys Gln Lys Glu Lys Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val
 40 80 85 90
 aca aca agc aaa cct gga gta tcc ttg gtc tac tcc atg ccc tcc cgg 458
 Thr Thr Ser Lys Pro Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg
 45 95 100 105
 aac ctg tcc ctg cgg ctg gag ggt ctc cag gag aaa gac tct ggc ccc 506
 50 Asn Leu Ser Leu Arg Leu Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro
 110 115 120
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 Tyr Ser Cys Ser Val Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly

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	Pro Ser Cys Arg Leu Gln Gly Val Pro His Val Gly Ala Asn Val Thr			
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	ctg agc tgc cag tct cca agg agt aag cct gct gtc caa tac cag tgg			698
20	Leu Ser Cys Gln Ser Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp			
		175	180	185
	gat cgg cag ctt cca tcc ttc cag act ttc ttt gca cca gca tta gat			746
25	Asp Arg Gln Leu Pro Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp			
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30	gtc atc cgt ggg tct tta agc ctc acc aac ctt tgg tct tcc atg gct			794
	Val Ile Arg Gly Ser Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala			
	205	210	215	
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40	220	225	230	235
	aat gtg acg ctg gaa gtg agc aca ggg cct gga gct gca gtg gtt gct			890
	Asn Val Thr Leu Glu Val Ser Thr Gly Pro Gly Ala Ala Val Val Ala			
45		240	245	250
	gga gct gtt gtg ggt acc ctg gtt gga ctg ggg ttg ctg gct ggg ctg			938
50	Gly Ala Val Val Gly Thr Leu Val Gly Leu Gly Leu Leu Ala Gly Leu			
		255	260	265
55	gtc ctc ttg tac cac cgc cgg ggc aag gcc ctg gag gag cca gcc aat			986

Val Leu Leu Tyr His Arg Arg Gly Lys Ala Leu Glu Glu Pro Ala Asn
5 270 275 280
gat atc aag gag gat gcc att gct ccc cgg acc ctg ccc tgg ccc aag 1034
Asp Ile Lys Glu Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Pro Lys
10 285 290 295
agc tca gac aca atc tcc aag aat ggg acc ctt tcc tct gtc acc tcc 1082
Ser Ser Asp Thr Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser
15 300 305 310 315
gca cga gcc ctc tgg cca ccc cat ggc cct ccc agg cct ggt gca ttg 1130
Ala Arg Ala Leu Trp Pro Pro His Gly Pro Pro Arg Pro Gly Ala Leu
320 325 330
25 acc ccc gcg ccc agt ctc tcc agc cag gcc ctg ccc tca cca aga ctg 1178
Thr Pro Thr Pro Ser Leu Ser Ser Gln Ala Leu Pro Ser Pro Arg Leu
335 340 345
30 ccc acg aca gat ggg gcc cac cct caa cca ata tcc ccc atc cct ggt 1226
Pro Thr Thr Asp Gly Ala His Pro Gln Pro Ile Ser Pro Ile Pro Gly
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Gly Val Ser Ser Ser Gly Leu Ser Arg Met Gly Ala Val Pro Val Met
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glg cct gcc cag agt caa gct ggc tct ctg gta tgaagacccc accactcatt 1327
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 Leu His Leu Pro Ala Asn Arg Leu Gln Ala Val Glu Gly Gly Glu Val
 35 35 40 45
 Val Leu Pro Ala Trp Tyr Thr Leu His Gly Glu Val Ser Ser Ser Gln
 40 50 55 60
 Pro Trp Glu Val Pro Phe Val Met Trp Phe Phe Lys Gln Lys Glu Lys
 65 70 75 80
 45 Glu Asp Gln Val Leu Ser Tyr Ile Asn Gly Val Thr Thr Ser Lys Pro
 85 90 95
 50 Gly Val Ser Leu Val Tyr Ser Met Pro Ser Arg Asn Leu Ser Leu Arg
 100 105 110
 55 Leu Glu Gly Leu Gln Glu Lys Asp Ser Gly Pro Tyr Ser Cys Ser Val
 115 120 125

5 Asn Val Gln Asp Lys Gln Gly Lys Ser Arg Gly His Ser Ile Lys Thr
 130 135 140
 Leu Glu Leu Asn Val Leu Val Pro Pro Ala Pro Pro Ser Cys Arg Leu
 10 145 150 155 160
 Gln Gly Val Pro His Val Gly Ala Asn Val Thr Leu Ser Cys Gln Ser
 15 165 170 175
 Pro Arg Ser Lys Pro Ala Val Gln Tyr Gln Trp Asp Arg Gln Leu Pro
 180 185 190
 20 Ser Phe Gln Thr Phe Phe Ala Pro Ala Leu Asp Val Ile Arg Gly Ser
 195 200 205
 25 Leu Ser Leu Thr Asn Leu Ser Ser Ser Met Ala Gly Val Tyr Val Cys
 210 215 220
 Lys Ala His Asn Glu Val Gly Thr Ala Gln Cys Asn Val Thr Leu Glu
 30 225 230 235 240
 Val Ser Thr Gly Pro Gly Ala Ala Val Val Ala Gly Ala Val Val Gly
 35 245 250 255
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 40 Arg Arg Gly Lys Ala Leu Glu Glu Pro Ala Asn Asp Ile Lys Glu Asp
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 45 Ala Ile Ala Pro Arg Thr Leu Pro Trp Pro Lys Ser Ser Asp Thr Ile
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 50 Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala Leu Trp
 305 310 315 320
 Pro Pro His Gly Pro Pro Arg Pro Gly Ala Leu Thr Pro Thr Pro Ser
 55 325 330 335

Leu Ser Ser Gln Ala Leu Pro Ser Pro Arg Leu Pro Thr Thr Asp Gly

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Ala His Pro Gln Pro Ile Ser Pro Ile Pro Gly Gly Val Ser Ser Ser

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Met Lys Lys Gln Phe Asn Arg Met Lys Gln

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ctg gct aac cag acc gtg ggc aga gct gag aaa aca gaa gtc ctt agt 161

Leu Ala Asn Gln Thr Val Gly Arg Ala Glu Lys Thr Glu Val Leu Ser

25

gaa gat cta tta cag att gag aga cgc ctg gac acg glg cgg tca ata 209

Glu Asp Leu Leu Gln Ile Glu Arg Arg Leu Asp Thr Val Arg Ser Ile

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tgc cac cat tcc cat aag cgc ttg gtg gca tgt ttc cag ggc cag cat 257
 Cys His His Ser His Lys Arg Leu Val Ala Cys Phe Gln Gly Gln His
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 60 65 70
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 15 Ala Gln Asn Met Gln Glu Ala Ser Thr Gln Leu Glu Asp Ser Leu Leu
 75 80 85 90
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 20 Gly Lys Met Leu Glu Thr Cys Gly Asp Ala Glu Asn Gln Leu Ala Leu
 25 95 100 105
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 30 Glu Leu Ser Gln His Glu Val Phe Val Glu Lys Glu Ile Val Asp Pro
 110 115 120
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 35 Leu Tyr Gly Ile Ala Glu Val Glu Ile Pro Asn Ile Gln Lys Gln Arg
 125 130 135
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 40 Lys Gln Leu Ala Arg Leu Val Leu Asp Trp Asp Ser Val Arg Ala Arg
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 45 Trp Asn Gln Ala His Lys Ser Ser Gly Thr Asn Phe Gln Gly Leu Pro
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 175 180 185

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 10 Ala Lys Glu Gly Glu Tyr Gly Lys Phe Phe Val Thr Leu Leu Glu Ala
 205 210 215
 caa gca gat tac cat aga aaa gca tta gca gtc tta gaa aag acc ctc 785
 15 Gln Ala Asp Tyr His Arg Lys Ala Leu Ala Val Leu Glu Lys Thr Leu
 220 225 230
 ccc gaa atg cga gcc cat caa gat aag tgg gcg gaa aaa cca gcc ttt 833
 20 Pro Glu Met Arg Ala His Gln Asp Lys Trp Ala Glu Lys Pro Ala Phe
 235 240 245 250
 ggg act ccc cta gaa gaa cac ctg aag agg agc ggg cgc gag att gcg 881
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 255 260 265
 ctg ccc att gaa gcc tgt gtc atg ctg ctt ctg gag aca ggc atg aag 929
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 40 Leu Lys Ala Ala Leu Asp Cys Ser Thr Ser His Leu Asp Glu Phe Tyr
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 tca gac ccc cat gct gta gca ggt gct tta aaa tcc tat tta cgg gaa 1073
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10	glt gca agt gtg cag gat caa gac aaa aaa ctt caa gac ttg tgg aga	1169			
	Val Ala Ser Val Gln Asp Gln Asp Lys Lys Leu Gln Asp Leu Trp Arg				
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	aca tgt cag aag ttg cca cca caa aat ttt gtt aac ttt aga tat ttg	1217			
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25	atc aag ttc ctt gca aag ctt gct cag acc agc gat gtg aat aaa atg	1265			
	Ile Lys Phe Leu Ala Lys Leu Ala Gln Thr Ser Asp Val Asn Lys Met				
		380	385	390	
30	act ccc agc aac att gcg att glg tta ggc cct aac ttg tta tgg gcc	1313			
	Thr Pro Ser Asn Ile Ala Ile Val Leu Gly Pro Asn Leu Leu Trp Ala				
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35	aga aat gaa gga aca ctt gct gaa atg gca gca gcc aca tcc gtc cat	1361			
	Arg Asn Glu Gly Thr Leu Ala Glu Met Ala Ala Ala Thr Ser Val His				
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	gac ttg gtg aag aag gaa agc ttt ggt gtg aag ctt atg gac ttc cag	1601		
	Asp Leu Val Lys Lys Glu Ser Phe Gly Val Lys Leu Met Asp Phe Gln			
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	gcc cac cgg cgg ggt ggc act cta aat aga aag cac ata tcc ccc gct	1649		
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25	ttc cag ccg cca ctt ccg ccc aca gat ggc agc acc gtg gtg ccc gct	1697		
	Phe Gln Pro Pro Leu Pro Pro Thr Asp Gly Ser Thr Val Val Pro Ala			
	525	530	535	
30	ggc cca gag ccc cct ccc cag agc tct agg gct gaa agc agc tct ggg	1745		
	Gly Pro Glu Pro Pro Pro Gln Ser Ser Arg Ala Glu Ser Ser Ser Gly			
35	540	545	550	
	ggt ggg act gtc ccc tct tcc gcg ggc ata ctg gag cag ggg ccg agc	1793		
	Gly Gly Thr Val Pro Ser Ser Ala Gly Ile Leu Glu Gln Gly Pro Ser			
40	555	560	565	570
	cca ggc gac ggc agt cct ccc aaa ccg aag gac cct gla tct gca gct	1841		
45	Pro Gly Asp Gly Ser Pro Pro Lys Pro Lys Asp Pro Val Ser Ala Ala			
	575	580	585	
50	gtg cca gca cca ggg aga aac aac agt cag ata gca tct ggc caa aat	1889		
	Val Pro Ala Pro Gly Arg Asn Asn Ser Gln Ile Ala Ser Gly Gln Asn			
	590	595	600	
55	cag ccc cag gca gct gct ggc tcc cac cag ctc tcc atg ggc caa cct	1937		

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Gln Pro Gln Ala Ala Ala Gly Ser His Gln Leu Ser Met Gly Gln Pro
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His Asn Ala Ala Gly Pro Ser Pro His Thr Leu Arg Arg Ala Val Lys
10 620 625 630
aaa ccc gct cca gca ccc ccg aaa ccg ggc aac cca cct cct ggc cac 2033
15 Lys Pro Ala Pro Ala Pro Pro Lys Pro Gly Asn Pro Pro Pro Gly His
635 640 645 650
ccc ggg ggc cag agt tct tca gga aca tct cag cat cca ccc agt ctg 2081
20 Pro Gly Gly Gln Ser Ser Ser Gly Thr Ser Gln His Pro Pro Ser Leu
655 660 665
25 tca cca gag cca ccc acc cga agc ccc tct cct ccc acc cag cac acg 2129
Ser Pro Lys Pro Pro Thr Arg Ser Pro Ser Pro Pro Thr Gln His Thr
30 670 675 680
ggc cag cct cca ggc cag ccc tcc gcc ccc tcc cag ctg tca gca ccc 2177
Gly Gln Pro Pro Gly Gln Pro Ser Ala Pro Ser Gln Leu Ser Ala Pro
35 685 690 695
cgg agg tac tcc agc agc ttg tct cca atc caa gct ccc aat cac cca 2225
40 Arg Arg Tyr Ser Ser Ser Leu Ser Pro Ile Gln Ala Pro Asn His Pro
700 705 710
ccg ccg cag ccc cct acg cag gcc acg cca ctg alg cac acc aaa ccc 2273
45 Pro Pro Gln Pro Pro Thr Gln Ala Thr Pro Leu Met His Thr Lys Pro
715 720 725 730
50 aat agc cag ggc cct ccc aac ccc alg gca ttg ccc agt gag cat gga 2321
Asn Ser Gln Gly Pro Pro Asn Pro Met Ala Leu Pro Ser Glu His Gly
55 735 740 745
cct gag cag cca tct cac acc cct ccc cag act cca acg ccc ccc agt 2369

Leu Glu Gln Pro Ser His Thr Pro Pro Gln Thr Pro Thr Pro Pro Ser
 5 750 755 760
 act ccg ccc cta gga aaa cag aac ccc agt ctg cca gct cct cag acc 2417
 Thr Pro Pro Leu Gly Lys Gln Asn Pro Ser Leu Pro Ala Pro Gln Thr
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 ctg gca ggg ggt aac cct gaa act gca cag cca cat gct gga acc tta 2465
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 780 785 790
 20 ccg aga ccg aga cca gla cca aag cca agg aac cgg ccc agc gtg ccc 2513
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 795 800 805 810
 25 cca ccc ccc caa cct cct ggt gtc cac tca gct ggg gac agc agc ctc 2561
 Pro Pro Pro Gln Pro Pro Gly Val His Ser Ala Gly Asp Ser Ser Leu
 30 815 820 825
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 35 Thr Asn Thr Ala Pro Thr Ala Ser Lys Ile Val Thr Asp Ser Asn Ser
 830 835 840
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 40 Arg Val Ser Glu Pro His Arg Ser Ile Phe Pro Glu Met His Ser Asp
 845 850 855
 45 tca gcc agc aaa gac gig cct ggc cgc aic ctg ctg gat ata gac aat 2705
 Ser Ala Ser Lys Asp Val Pro Gly Arg Ile Leu Leu Asp Ile Asp Asn
 860 865 870
 50 gat acc gag agc act gcc ctg igaagaaagc cctttccag ccttccacca 2756
 Asp Thr Glu Ser Thr Ala Leu
 55 875 880

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 5 gaaaagcttt cagtgaggga caaaggaggg cctcacigtg cgggaccigg ccttcgtcac 2876
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<210> 146

<211> 881

<212> PRT

<213> Homo sapiens

<400> 146

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Gly Arg Ala Glu Lys Thr Glu Val Leu Ser Glu Asp Leu Leu Gln Ile

20 25 30

Glu Arg Arg Leu Asp Thr Val Arg Ser Ile Cys His His Ser His Lys

35 40 45

Arg Leu Val Ala Cys Phe Gln Gly Gln His Gly Thr Asp Ala Glu Arg

50 55 60

Arg His Lys Lys Leu Pro Leu Thr Ala Leu Ala Gln Asn Met Gln Glu

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	65	70	75	80
5	Ala Ser Thr Gln Leu Glu Asp Ser Leu Leu Gly Lys Met Leu Glu Thr			
	85	90	95	
10	Cys Gly Asp Ala Glu Asn Gln Leu Ala Leu Glu Leu Ser Gln His Glu			
	100	105	110	
15	Val Phe Val Glu Lys Glu Ile Val Asp Pro Leu Tyr Gly Ile Ala Glu			
	115	120	125	
	Val Glu Ile Pro Asn Ile Gln Lys Gln Arg Lys Gln Leu Ala Arg Leu			
20	130	135	140	
	Val Leu Asp Trp Asp Ser Val Arg Ala Arg Trp Asn Gln Ala His Lys			
	145	150	155	160
25	Ser Ser Gly Thr Asn Phe Gln Gly Leu Pro Ser Lys Ile Asp Thr Leu			
	165	170	175	
30	Lys Glu Glu Met Asp Glu Ala Gly Asn Lys Val Glu Gln Cys Lys Asp			
	180	185	190	
	Gln Leu Ala Ala Asp Met Tyr Asn Phe Met Ala Lys Glu Gly Glu Tyr			
35	195	200	205	
	Gly Lys Phe Phe Val Thr Leu Leu Glu Ala Gln Ala Asp Tyr His Arg			
40	210	215	220	
	Lys Ala Leu Ala Val Leu Glu Lys Thr Leu Pro Glu Met Arg Ala His			
	225	230	235	240
45	Gln Asp Lys Trp Ala Glu Lys Pro Ala Phe Gly Thr Pro Leu Glu Glu			
	245	250	255	
50	His Leu Lys Arg Ser Gly Arg Glu Ile Ala Leu Pro Ile Glu Ala Cys			
	260	265	270	
55	Val Met Leu Leu Leu Glu Thr Gly Met Lys Glu Glu Gly Leu Phe Arg			
	275	280	285	

Ile Gly Ala Gly Ala Ser Lys Leu Lys Lys Leu Lys Ala Ala Leu Asp
 5 290 295 300
 Cys Ser Thr Ser His Leu Asp Glu Phe Tyr Ser Asp Pro His Ala Val
 10 305 310 315 320
 Ala Gly Ala Leu Lys Ser Tyr Leu Arg Glu Leu Pro Glu Pro Leu Met
 325 330 335
 15 Thr Phe Asn Leu Tyr Glu Glu Trp Thr Gln Val Ala Ser Val Gln Asp
 340 345 350
 20 Gln Asp Lys Lys Leu Gln Asp Leu Trp Arg Thr Cys Gln Lys Leu Pro
 355 360 365
 25 Pro Gln Asn Phe Val Asn Phe Arg Tyr Leu Ile Lys Phe Leu Ala Lys
 370 375 380
 Leu Ala Gln Thr Ser Asp Val Asn Lys Met Thr Pro Ser Asn Ile Ala
 30 385 390 395 400
 Ile Val Leu Gly Pro Asn Leu Leu Trp Ala Arg Asn Glu Gly Thr Leu
 405 410 415
 35 Ala Glu Met Ala Ala Ala Thr Ser Val His Val Val Ala Val Ile Glu
 420 425 430
 40 Pro Ile Ile Gln His Ala Asp Trp Phe Phe Pro Glu Glu Val Glu Phe
 435 440 445
 45 Asn Val Ser Glu Ala Phe Val Pro Leu Thr Thr Pro Ser Ser Asn His
 450 455 460
 50 Ser Phe His Thr Gly Asn Asp Ser Asp Ser Gly Thr Leu Glu Arg Lys
 465 470 475 480
 Arg Pro Ala Ser Met Ala Val Met Glu Gly Asp Leu Val Lys Lys Glu
 55 485 490 495

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Ser Phe Gly Val Lys Leu Met Asp Phe Gln Ala His Arg Arg Gly Gly
 500 505 510
 5 Thr Leu Asn Arg Lys His Ile Ser Pro Ala Phe Gln Pro Pro Leu Pro
 515 520 525
 10 Pro Thr Asp Gly Ser Thr Val Val Pro Ala Gly Pro Glu Pro Pro Pro
 530 535 540
 15 Gln Ser Ser Arg Ala Glu Ser Ser Ser Gly Gly Gly Thr Val Pro Ser
 545 550 555 560
 Ser Ala Gly Ile Leu Glu Gln Gly Pro Ser Pro Gly Asp Gly Ser Pro
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 Pro Lys Pro Lys Asp Pro Val Ser Ala Ala Val Pro Ala Pro Gly Arg
 25 580 585 590
 Asn Asn Ser Gln Ile Ala Ser Gly Gln Asn Gln Pro Gln Ala Ala Ala
 595 600 605
 30 Gly Ser His Gln Leu Ser Met Gly Gln Pro His Asn Ala Ala Gly Pro
 610 615 620
 35 Ser Pro His Thr Leu Arg Arg Ala Val Lys Lys Pro Ala Pro Ala Pro
 625 630 635 640
 Pro Lys Pro Gly Asn Pro Pro Pro Gly His Pro Gly Gly Gln Ser Ser
 40 645 650 655
 Ser Gly Thr Ser Gln His Pro Pro Ser Leu Ser Pro Lys Pro Pro Thr
 45 660 665 670
 Arg Ser Pro Ser Pro Pro Thr Gln His Thr Gly Gln Pro Pro Gly Gln
 675 680 685
 50 Pro Ser Ala Pro Ser Gln Leu Ser Ala Pro Arg Arg Tyr Ser Ser Ser
 690 695 700
 55 Leu Ser Pro Ile Gln Ala Pro Asn His Pro Pro Pro Gln Pro Pro Thr

705 710 715 720
 5 Gln Ala Thr Pro Leu Met His Thr Lys Pro Asn Ser Gln Gly Pro Pro
 725 730 735
 10 Asn Pro Met Ala Leu Pro Ser Glu His Gly Leu Glu Gln Pro Ser His
 740 745 750
 15 Thr Pro Pro Gln Thr Pro Thr Pro Pro Ser Thr Pro Pro Leu Gly Lys
 755 760 765
 20 Gln Asn Pro Ser Leu Pro Ala Pro Gln Thr Leu Ala Gly Gly Asn Pro
 770 775 780
 25 Glu Thr Ala Gln Pro His Ala Gly Thr Leu Pro Arg Pro Arg Pro Val
 785 790 795 800
 30 Pro Lys Pro Arg Asn Arg Pro Ser Val Pro Pro Pro Pro Gln Pro Pro
 805 810 815
 35 Gly Val His Ser Ala Gly Asp Ser Ser Leu Thr Asn Thr Ala Pro Thr
 820 825 830
 40 Ala Ser Lys Ile Val Thr Asp Ser Asn Ser Arg Val Ser Glu Pro His
 835 840 845
 45 Arg Ser Ile Phe Pro Glu Met His Ser Asp Ser Ala Ser Lys Asp Val
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<220>

<221> CDS

<222> (140).. (1105)

<400> 147

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 ctctgctaag accgtgcc atg cca gtc acg gla acc cgc acc acc atc aca 172

Met Pro Val Thr Val Thr Arg Thr Thr Ile Thr

1 5 10

acc acc acg acg tca tct tcg ggc ctg ggg tcc ccc atg atc gtg ggg 220

Thr Thr Thr Thr Ser Ser Ser Gly Leu Gly Ser Pro Met Ile Val Gly

15 20 25

tcc cct cgg gcc ctg aca cag ccc ctg ggt ctg ctt cgc ctg ctg cag 268

Ser Pro Arg Ala Leu Thr Gln Pro Leu Gly Leu Leu Arg Leu Leu Gln

30 35 40

ctg gtg tct acc tgc gtg gcc ttc tcg ctg gtg gct agc gtg ggc gcc 316

Leu Val Ser Thr Cys Val Ala Phe Ser Leu Val Ala Ser Val Gly Ala

45 50 55

tgg acg ggg tcc atg ggc aac tgg tcc atg ttc acc tgg tgc ttc tgc 364

Trp Thr Gly Ser Met Gly Asn Trp Ser Met Phe Thr Trp Cys Phe Cys

60 65 70 75

ttc tcc gtg acc ctg atc atc ctg atc gtg gag ctg tgc ggg ctg cag 412

Phe Ser Val Thr Leu Ile Ile Leu Ile Val Glu Leu Cys Gly Leu Gln

80 85 90

gcc cgc ttc ccc ctg tct tgg cgc aac ttc ccc atc acc ttc gcc tgc 460

Ala Arg Phe Pro Leu Ser Trp Arg Asn Phe Pro Ile Thr Phe Ala Cys

	95	100	105	
5	tat gcg ggc ctc ttc tgc ctc tgc gcc tcc atc atc tac ccc acc acc 508			
	Tyr Ala Gly Leu Phe Cys Leu Ser Ala Ser Ile Ile Tyr Pro Thr Thr			
	110	115	120	
10	tat gtc cag ttc ctg tcc cac ggc cgt tgc cgg gac cac gcc atc gcc 556			
	Tyr Val Gln Phe Leu Ser His Gly Arg Ser Arg Asp His Ala Ile Ala			
15	125	130	135	
	gcc acc ttc ttc tcc tgc atc gcg tgt gtg gct tac gcc acc gaa gtg 604			
20	Ala Thr Phe Phe Ser Cys Ile Ala Cys Val Ala Tyr Ala Thr Glu Val			
	140	145	150	155
	gcc tgg acc cgg gcc cgg ccc ggc gag atc act ggc tat atg gcc acc 652			
25	Ala Trp Thr Arg Ala Arg Pro Gly Glu Ile Thr Gly Tyr Met Ala Thr			
	160	165	170	
30	gla ccc ggg ctg ctg aag gtg ctg gag acc ttc gtt gcc tgc atc atc 700			
	Val Pro Gly Leu Leu Lys Val Leu Glu Thr Phe Val Ala Cys Ile Ile			
	175	180	185	
35	ttc gcg ttc atc agc gac ccc aac ctg tac cag cac cag ccg gcc ctg 748			
	Phe Ala Phe Ile Ser Asp Pro Asn Leu Tyr Gln His Gln Pro Ala Leu			
40	190	195	200	
	gag tgg tgc gtg gcg gtg tac gcc atc tgc ttc atc cta gcg gcc atc 796			
	Glu Trp Cys Val Ala Val Tyr Ala Ile Cys Phe Ile Leu Ala Ala Ile			
45	205	210	215	
	gcc atc ctg ctg aac ctg ggg gag tgc acc aac gtg cta ccc atc ccc 844			
50	Ala Ile Leu Leu Asn Leu Gly Glu Cys Thr Asn Val Leu Pro Ile Pro			
	220	225	230	235
55	ttc ccc agc ttc ctg tgc ggg ctg gcc ttg ctg tct gtc ctc ctc tat 892			
	Phe Pro Ser Phe Leu Ser Gly Leu Ala Leu Leu Ser Val Leu Leu Tyr			

240 245 250
 5 gcc acc gcc ctt gtt ctc tgg ccc ctc tac cag ttc gat gag aag tat 940
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 255 260 265
 10 ggc ggc cag cct cgg cgc tcg aga gat gla agc tgc agc cgc agc cat 988
 Gly Gly Gln Pro Arg Arg Ser Arg Asp Val Ser Cys Ser Arg Ser His
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 15 gcc tac tac gtg tgt gcc tgg gac cgc cga ctg gct gtg gcc atc ctg 1036
 Ala Tyr Tyr Val Cys Ala Trp Asp Arg Arg Leu Ala Val Ala Ile Leu
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 20 acg gcc atc aac cta ctg gcg tat gtg gct gac ctg gtg cac tct gcc 1084
 Thr Ala Ile Asn Leu Leu Ala Tyr Val Ala Asp Leu Val His Ser Ala
 300 305 310 315
 30 cac ctg gtt ttt gtc aag gtc taagactctc ccaagaggct cccgttcct 1135
 His Leu Val Phe Val Lys Val
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<211> 322

<212> PRT

<213> Homo sapiens

<400> 148

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					20					25					30	
15	Thr	Gln	Pro	Leu	Gly	Leu	Leu	Arg	Leu	Leu	Gln	Leu	Val	Ser	Thr	Cys
					35					40					45	
20	Val	Ala	Phe	Ser	Leu	Val	Ala	Ser	Val	Gly	Ala	Trp	Thr	Gly	Ser	Met
					50					55					60	
25	Gly	Asn	Trp	Ser	Met	Phe	Thr	Trp	Cys	Phe	Cys	Phe	Ser	Val	Thr	Leu
					65					70					75	
30	Ile	Ile	Leu	Ile	Val	Glu	Leu	Cys	Gly	Leu	Gln	Ala	Arg	Phe	Pro	Leu
										85					90	
35	Ser	Trp	Arg	Asn	Phe	Pro	Ile	Thr	Phe	Ala	Cys	Tyr	Ala	Gly	Leu	Phe
										100					105	
40	Cys	Leu	Ser	Ala	Ser	Ile	Ile	Tyr	Pro	Thr	Thr	Tyr	Val	Gln	Phe	Leu
										115					120	
45	Ser	His	Gly	Arg	Ser	Arg	Asp	His	Ala	Ile	Ala	Ala	Thr	Phe	Phe	Ser
										130					135	
50	Cys	Ile	Ala	Cys	Val	Ala	Tyr	Ala	Thr	Glu	Val	Ala	Trp	Thr	Arg	Ala
										145					150	
55	Arg	Pro	Gly	Glu	Ile	Thr	Gly	Tyr	Met	Ala	Thr	Val	Pro	Gly	Leu	Leu
										165					170	
	Lys	Val	Leu	Glu	Thr	Phe	Val	Ala	Cys	Ile	Ile	Phe	Ala	Phe	Ile	Ser
										180					185	
	Asp	Pro	Asn	Leu	Tyr	Gln	His	Gln	Pro	Ala	Leu	Glu	Trp	Cys	Val	Ala
										195					200	
															205	

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Val Tyr Ala Ile Cys Phe Ile Leu Ala Ala Ile Ala Ile Leu Leu Asn
5 210 215 220

Leu Gly Glu Cys Thr Asn Val Leu Pro Ile Pro Phe Pro Ser Phe Leu
10 225 230 235 240

Ser Gly Leu Ala Leu Leu Ser Val Leu Leu Tyr Ala Thr Ala Leu Val
 245 250 255

Leu Trp Pro Leu Tyr Gln Phe Asp Glu Lys Tyr Gly Gly Gln Pro Arg
15 260 265 270

Arg Ser Arg Asp Val Ser Cys Ser Arg Ser His Ala Tyr Tyr Val Cys
20 275 280 285

Ala Trp Asp Arg Arg Leu Ala Val Ala Ile Leu Thr Ala Ile Asn Leu
25 290 ~ 295 300

Leu Ala Tyr Val Ala Asp Leu Val His Ser Ala His Leu Val Phe Val
30 305 310 315 320

Lys Val

35 <210> 149

 <211> 4409

 <212> DNA

40 <213> Homo sapiens

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45 <221> CDS

 <222> (39).. (2027)

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 Met Ser Trp Leu Ser Ser

55 1 5

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 5 Ser Gln Gly Val Val Leu Thr Ala Tyr His Pro Ser Gly Lys Asp Gln
 10 10 15 20
 gcc gtc ggg aac agc cat gca aag gca ggg gag gaa gcc acc tcg agt 152
 Ala Val Gly Asn Ser His Ala Lys Ala Gly Glu Glu Ala Thr Ser Ser
 25 30 35
 15 cgc aga tat ggc cag tac act atg aac cag gaa agc acc acc atc aaa 200
 Arg Arg Tyr Gly Gln Tyr Thr Met Asn Gln Glu Ser Thr Thr Ile Lys
 20 40 45 50
 gtt atg gag aag cct cca ttt gat cga tca att tcc cag gat tct ttg 248
 Val Met Glu Lys Pro Pro Phe Asp Arg Ser Ile Ser Gln Asp Ser Leu
 25 55 60 65 70
 gat gaa cta tct atg gaa gac tat tgg ata gaa cta gaa aac atc aag 296
 30 Asp Glu Leu Ser Met Glu Asp Tyr Trp Ile Glu Leu Glu Asn Ile Lys
 75 80 85
 35 aaa tct agt gaa aac agc caa gaa gat caa gag gtg gtt gtt gtc aaa 344
 Lys Ser Ser Glu Asn Ser Gln Glu Asp Gln Glu Val Val Val Val Lys
 90 95 100
 40 gag cct gat gag gga gaa ttg gaa gaa gag tgg ctt aaa gag gcc ggt 392
 Glu Pro Asp Glu Gly Glu Leu Glu Glu Glu Trp Leu Lys Glu Ala Gly
 45 105 110 115
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 50 Leu Ser Asn Leu Phe Gly Glu Ser Ala Gly Asp Pro Gln Glu Ser Ile
 120 125 130
 55 gtg ttt tta tca aca ttg acg cgg acc cag gca gca gca gtt cag aag 488
 Val Phe Leu Ser Thr Leu Thr Arg Thr Gln Ala Ala Ala Val Gln Lys

	135	140	145	150	
5	cga gta gag acg gtc tcc cag acc ttg agg aaa aaa aac aaa cag tac				536
	Arg Val Glu Thr Val Ser Gln Thr Leu Arg Lys Lys Asn Lys Gln Tyr				
	155	160	165		
10	cag att cct gac gtc aga gac ata ttt gct caa cag aga gaa tca aaa				584
	Gln Ile Pro Asp Val Arg Asp Ile Phe Ala Gln Gln Arg Glu Ser Lys				
15	170	175	180		
	gaa aca gct cca ggt ggc act gaa tcg cag tca ctt aga aca aat gaa				632
20	Glu Thr Ala Pro Gly Gly Thr Glu Ser Gln Ser Leu Arg Thr Asn Glu				
	185	190	195		
	aac aaa tac caa gga aga gat gac gag gca tct aac ctt gtt ggt gaa				680
25	Asn Lys Tyr Gln Gly Arg Asp Asp Glu Ala Ser Asn Leu Val Gly Glu				
	200	205	210		
30	gag aag ctg atc cca cct gag gag acg cct gcc cct gaa aca gac atc				728
	Glu Lys Leu Ile Pro Pro Glu Glu Thr Pro Ala Pro Glu Thr Asp Ile				
	215	220	225	230	
35	aac ctg gag gla tca ttt gcc gag caa gca ctg aat cag aaa gag agc				776
	Asn Leu Glu Val Ser Phe Ala Glu Gln Ala Leu Asn Gln Lys Glu Ser				
40	235	240	245		
	tcc aag gag aaa atc cag aag agc aaa ggc gat gat gcc aca tta cct				824
	Ser Lys Glu Lys Ile Gln Lys Ser Lys Gly Asp Asp Ala Thr Leu Pro				
45	250	255	260		
	agt ttc aga ttg cca aaa gac aaa acg ggt acc aca agg att ggt gac				872
50	Ser Phe Arg Leu Pro Lys Asp Lys Thr Gly Thr Thr Arg Ile Gly Asp				
	265	270	275		
55	ctc gca ccc cag gac atg aag aaa gtt tgc cat tta gcc cta att gag				920
	Leu Ala Pro Gln Asp Met Lys Lys Val Cys His Leu Ala Leu Ile Glu				

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	280	285	290	
5	ctg act gcc ctc tat gat gla ttg ggt att gag ctg aaa caa caa aaa			968
	Leu Thr Ala Leu Tyr Asp Val Leu Gly Ile Glu Leu Lys Gln Gln Lys			
	295	300	305	310
10	gct gtg aaa atc aaa aca aaa gat tct ggt ctt ttt tgc gtt cca ttg			1016
	Ala Val Lys Ile Lys Thr Lys Asp Ser Gly Leu Phe Cys Val Pro Leu			
15		315	320	325
	aca gcg cta tta gaa caa gat cag agg aaa gla cca gga atg cga ata			1064
20	Thr Ala Leu Leu Glu Gln Asp Gln Arg Lys Val Pro Gly Met Arg Ile			
		330	335	340
25	ccc ttg atc ttt caa aaa ctg att tct cga att gaa gag aga ggt ttg			1112
	Pro Leu Ile Phe Gln Lys Leu Ile Ser Arg Ile Glu Glu Arg Gly Leu			
		345	350	355
30	gaa aca gaa ggc ctc tta cgg atc cct gga gct gcc att aga atc aag			1160
	Glu Thr Glu Gly Leu Leu Arg Ile Pro Gly Ala Ala Ile Arg Ile Lys			
35		360	365	370
	aat ctt tgc caa gaa cta gaa gca aag ttt tat gaa ggg act ttt aat			1208
	Asn Leu Cys Gln Glu Leu Glu Ala Lys Phe Tyr Glu Gly Thr Phe Asn			
40		375	380	385
	390			
	tgg gaa agt gtc aaa cag cat gat gcc gcc agc ctg ctg aag ctc ttc			1256
45	Trp Glu Ser Val Lys Gln His Asp Ala Ala Ser Leu Leu Lys Leu Phe			
		395	400	405
50	att cgg gag ttg ccc cag cca ctg ctc agt gtg gag tat ctc aaa gcc			1304
	Ile Arg Glu Leu Pro Gln Pro Leu Leu Ser Val Glu Tyr Leu Lys Ala			
		410	415	420
55	ttt cag gct gtc cag aat ctt cca acc aag aag cag caa cta cag gct			1352

Phe Gln Ala Val Gln Asn Leu Pro Thr Lys Lys Gln Gln Leu Gln Ala
 5 425 430 435
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 Leu Asn Leu Leu Gly Ile Leu Leu Pro Asp Ala Asn Arg Asp Thr Leu
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 Lys Ala Leu Leu Glu Phe Leu Gln Arg Val Ile Asp Asn Lys Glu Lys
 15 455 460 465 470
 aat aaa atg aca gtc atg aat gta gca atg gtc atg gcc ccg aat ctc 1496
 20 Asn Lys Met Thr Val Met Asn Val Ala Met Val Met Ala Pro Asn Leu
 475 480 485
 25 ttt atg tgt cat gca ttg gga ttg aag tcc agt gaa cag cga gaa ttt 1544
 Phe Met Cys His Ala Leu Gly Leu Lys Ser Ser Glu Gln Arg Glu Phe
 490 495 500
 30 gla atg gca gct ggg aca gca aat acc atg cac tta ttg att aag tac 1592
 Val Met Ala Ala Gly Thr Ala Asn Thr Met His Leu Leu Ile Lys Tyr
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Glu Ser Thr Thr Ile Lys Val Met Glu Lys Pro Pro Phe Asp Arg Ser

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Ile Ser Gln Asp Ser Leu Asp Glu Leu Ser Met Glu Asp Tyr Trp Ile

65 70 75 80

Glu Leu Glu Asn Ile Lys Lys Ser Ser Glu Asn Ser Gln Glu Asp Gln

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35 40 45

Lys Lys Val Pro Gly Arg Met Tyr Ser Asn Asn Pro Phe Trp Asn Gly

40 50 55 60

Val Gln Thr Asn Pro Phe Leu Asn Gly Asn Val Pro Val Met Pro Ser

65 70 75 80

45 Leu Asp Glu Leu Asn Pro Lys Ser Thr Val Asp Leu Leu Leu Phe Asp

85 90 95

50 Ala Gly Thr Ser Ser Phe Thr Glu Ser Ser Ser Ala Thr Thr Asn Ser

100 105 110

55 Thr Gly Asn Ile Phe Asp Glu Leu Pro Val Thr Asn Gly Leu His Ala

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5	Glu Pro Pro Val Arg Arg Asp Asn Pro Phe Phe Arg Ser Lys Arg Ser			
	130	135	140	
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	145	150	155	160
	Thr Ser Ser Ser Phe Phe Thr Gly Leu Lys Ser Pro Ala Pro Glu Gln			
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	Phe Gln Ser Arg Glu Asp Phe Arg Thr Ala Trp Leu Asn His Arg Lys			
20		180	185	190
	Leu Ala Arg Ser Cys His Asp Leu Asp Leu Leu Gly Gln Ser Pro Gly			
	195	200	205	
25	Trp Gly Gln Thr Gln Ala Val Glu Thr Asn Ile Val Cys Lys Leu Asp			
	210	215	220	
30	Ser Ser Gly Gly Ala Val Gln Leu Pro Asp Thr Ser Ile Ser Ile His			
	225	230	235	240
	Val Pro Glu Gly His Val Ala Pro Gly Glu Thr Gln Gln Ile Ser Met			
35		245	250	255
	Lys Ala Leu Leu Asp Pro Pro Leu Glu Leu Asn Ser Asp Arg Ser Cys			
40		260	265	270
	Ser Ile Ser Pro Val Leu Glu Val Lys Leu Ser Asn Leu Glu Val Lys			
	275	280	285	
45	Thr Ser Ile Ile Leu Glu Met Lys Val Ser Ala Glu Ile Lys Asn Asp			
	290	295	300	
50	Leu Phe Ser Lys Ser Thr Val Gly Leu Gln Cys Leu Arg Ser Asp Ser			
	305	310	315	320
	Lys Glu Gly Pro Tyr Val Ser Val Pro Leu Asn Cys Ser Cys Gly Asp			
55		325	330	335

5	Thr Val Gln Ala Gln Leu His Asn Leu Glu Pro Cys Met Tyr Val Ala	340	345	350
10	Val Val Ala His Gly Pro Ser Ile Leu Tyr Pro Ser Thr Val Trp Asp	355	360	365
15	Phe Ile Asn Lys Lys Val Thr Val Gly Leu Tyr Gly Pro Lys His Ile	370	375	380
20	His Pro Ser Phe Lys Thr Val Val Thr Ile Phe Gly His Asp Cys Ala	385	390	395
25	Pro Lys Thr Leu Leu Val Ser Glu Val Thr Arg Gln Ala Pro Asn Pro	405	410	415
30	Ala Pro Val Ala Leu Gln Leu Trp Gly Lys His Gln Phe Val Leu Ser	- 420	425	430
35	Arg Pro Gln Asp Leu Lys Val Cys Met Phe Ser Asn Met Thr Asn Tyr	435	440	445
40	Glu Val Lys Ala Ser Glu Gln Ala Lys Val Val Arg Gly Phe Gln Leu	450	455	460
45	Lys Leu Gly Lys Val Ser Arg Leu Ile Phe Pro Ile Thr Ser Gln Asn	465	470	475
50	Pro Asn Glu Leu Ser Asp Phe Thr Leu Arg Val Gln Val Lys Asp Asp	485	490	495
55	Gln Glu Ala Ile Leu Thr Gln Phe Cys Val Gln Thr Pro Gln Pro Pro	500	505	510
	Pro Lys Ser Ala Ile Lys Pro Ser Gly Gln Arg Arg Phe Leu Lys Lys	515	520	525
	Asn Glu Val Gly Lys Ile Ile Leu Ser Pro Phe Ala Thr Thr Thr Lys	530	535	540

Tyr Pro Thr Phe Gln Asp Arg Pro Val Ser Ser Leu Lys Phe Gly Lys
 5 545 550 555 560
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 Tyr Lys Lys Gly Asp Gly Ile Ala Leu Leu Ser Glu Glu Arg Val Arg
 580 585 590
 15 Leu Arg Gly Gln Leu Trp Thr Lys Glu Trp Tyr Ile Gly Tyr Tyr Gln
 595 600 605
 20 Gly Arg Val Gly Leu Val His Thr Lys Asn Val Leu Val Val Gly Arg
 610 615 620
 Ala Arg Pro Ser Leu Cys Ser Gly Pro Glu Leu Ser Thr Ser Val Leu
 25 625 630 635 640
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 30 645 650 655
 Ser Val Arg Thr Leu Leu Met Glu Asn Ile Ser Ser Trp Arg Ser Phe
 660 665 670
 35 Ala Asp Ala Leu Gly Tyr Val Asn Leu Pro Leu Thr Phe Phe Cys Arg
 675 680 685
 40 Ala Glu Leu Asp Ser Glu Pro Glu Arg Val Ala Ser Val Leu Glu Lys
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 45 705 710 715 720
 Gln Lys Glu Leu Val Met Ala Leu Leu Lys Met Asp Cys Gln Gly Leu
 50 725 730 735
 Val Val Arg Leu Ile Gln Asp Phe Val Leu Leu Thr Thr Ala Val Glu
 740 745 750
 55 Val Ala Gln Arg Trp Arg Glu Leu Ala Glu Lys Leu Ala Lys Val Ser

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5 755 760 765
 Lys Gln Gln Met Asp Ala Tyr Glu Ser Pro His Arg Asp Arg Asn Gly
 770 775 780
 10 Val Val Asp Ser Glu Ala Met Trp Lys Pro Ala Tyr Asp Phe Leu Leu
 785 790 795 800
 15 Thr Trp Ser His Gln Ile Gly Asp Ser Tyr Arg Asp Val Ile Gln Glu
 805 810 815
 Leu His Leu Gly Leu Asp Lys Met Lys Asn Pro Ile Thr Lys Arg Trp
 20 820 825 830
 Lys His Leu Thr Gly Thr Leu Ile Leu Val Asn Ser Leu Asp Val Leu
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 gcgggcgccg gc alg tgg ctg lgg gag gac cag ggc ggc ctc ctg ggc cct 171
 Met Trp Leu Trp Glu Asp Gln Gly Gly Leu Leu Gly Pro
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 5 Phe Ser Phe Leu Leu Leu Val Leu Leu Leu Val Thr Arg Ser Pro Val
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 10 Asn Ala Cys Leu Leu Thr Gly Ser Leu Phe Val Leu Leu Arg Val Phe
 30 35 40 45
 15 agc ttt gag ccg gtg ccc tct tgc agg gcc ctg cag gtg ctc aag ccc 315
 Ser Phe Glu Pro Val Pro Ser Cys Arg Ala Leu Gln Val Leu Lys Pro
 20 50 55 60
 cgg gac cgc att tct gcc atc gcc cac cgt ggc ggc agc cac gac gcg 363
 Arg Asp Arg Ile Ser Ala Ile Ala His Arg Gly Gly Ser His Asp Ala
 25 65 70 75
 ccc gag aac acg ctg gcg gcc att cgg cag gca gct aag aat gga gca 411
 30 Pro Glu Asn Thr Leu Ala Ala Ile Arg Gln Ala Ala Lys Asn Gly Ala
 80 85 90
 35 aca ggc gtg gag tlg gac att gag ttt act tct gac ggg att cct gtc 459
 Thr Gly Val Glu Leu Asp Ile Glu Phe Thr Ser Asp Gly Ile Pro Val
 95 100 105
 40 tta atg cac gat aac aca gta gat agg acg act gat ggg act ggg cga 507
 Leu Met His Asp Asn Thr Val Asp Arg Thr Thr Asp Gly Thr Gly Arg
 110 115 120 125
 45 ttg tgt gat ttg aca ttt gaa caa att agg aag ctg aat cct gca gca 555
 Leu Cys Asp Leu Thr Phe Glu Gln Ile Arg Lys Leu Asn Pro Ala Ala
 50 130 135 140
 aac cac aga ctc agg aat gat ttc cct gat gaa aag atc cct acc cta 603
 55 Asn His Arg Leu Arg Asn Asp Phe Pro Asp Glu Lys Ile Pro Thr Leu

	145	150	155	
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	Arg Glu Ala Val Ala Glu Cys Leu Asn His Asn Leu Thr Ile Phe Phe			
	160	165	170	
10	gat gtc aaa ggc cat gca cac aag gct act gag gct cta aag aaa atg	699		
	Asp Val Lys Gly His Ala His Lys Ala Thr Glu Ala Leu Lys Lys Met			
15	175	180	185	
	tat atg gaa ttt cct caa ctg tat aat aat agt gtg gtc tgt tct ttc	747		
	Tyr Met Glu Phe Pro Gln Leu Tyr Asn Asn Ser Val Val Cys Ser Phe			
20	190	195	200	205
	ttg cca gaa gtt atc tac aag atg aga caa aca gat cgg gat gta ata	795		
25	Leu Pro Glu Val Ile Tyr Lys Met Arg Gln Thr Asp Arg Asp Val Ile			
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30	aca gca tta act cac aga cct tgg agc cta agc cat aca gga gat ggg	843		
	Thr Ala Leu Thr His Arg Pro Trp Ser Leu Ser His Thr Gly Asp Gly			
	225	230	235	
35	aaa cca cgc tat gat act ttc tgg aaa cat ttt ata ttt gtt atg atg	891		
	Lys Pro Arg Tyr Asp Thr Phe Trp Lys His Phe Ile Phe Val Met Met			
	240	245	250	
40	gac att ttg ctc gat tgg agc atg cat aat atc ttg tgg tac ctg tgt	939		
	Asp Ile Leu Leu Asp Trp Ser Met His Asn Ile Leu Trp Tyr Leu Cys			
45	255	260	265	
	gga att tca gct ttc ctc atg caa aag gat ttt gta tcc ccg gcc tac	987		
	Gly Ile Ser Ala Phe Leu Met Gln Lys Asp Phe Val Ser Pro Ala Tyr			
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	ttg aag aag tgg tca gct aaa gga atc cag gtt gtt ggt tgg act gtt	1035		
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Leu Leu Thr Gly Ser Leu Phe Val Leu Leu Arg Val Phe Ser Phe Glu

35 40 45

Pro Val Pro Ser Cys Arg Ala Leu Gln Val Leu Lys Pro Arg Asp Arg

50 - 55 60

Ile Ser Ala Ile Ala His Arg Gly Gly Ser His Asp Ala Pro Glu Asn

65 70 75 80

Thr Leu Ala Ala Ile Arg Gln Ala Ala Lys Asn Gly Ala Thr Gly Val

85 90 95

Glu Leu Asp Ile Glu Phe Thr Ser Asp Gly Ile Pro Val Leu Met His

100 105 110

Asp Asn Thr Val Asp Arg Thr Thr Asp Gly Thr Gly Arg Leu Cys Asp

115 120 125

Leu Thr Phe Glu Gln Ile Arg Lys Leu Asn Pro Ala Ala Asn His Arg

130 135 140

Leu Arg Asn Asp Phe Pro Asp Glu Lys Ile Pro Thr Leu Arg Glu Ala

145 150 155 160

Val Ala Glu Cys Leu Asn His Asn Leu Thr Ile Phe Phe Asp Val Lys

165 170 175

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Gly His Ala His Lys Ala Thr Glu Ala Leu Lys Lys Met Tyr Met Glu
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 Phe Pro Gln Leu Tyr Asn Asn Ser Val Val Cys Ser Phe Leu Pro Glu
 195 200 205
 Val Ile Tyr Lys Met Arg Gln Thr Asp Arg Asp Val Ile Thr Ala Leu
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 225 230 235 240
 Tyr Asp Thr Phe Trp Lys His Phe Ile Phe Val Met Met Asp Ile Leu
 245 250 255
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 260 265 270
 Ala Phe Leu Met Gln Lys Asp Phe Val Ser Pro Ala Tyr Leu Lys Lys
 275 280 285
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Gln Arg Val Gly Ala Ala Ala Ser Arg Gly Ala Asp Asp Ala Met Glu

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agc agc aag cct ggt cca glg cag gtt gtt ttg gtt cag aaa gat caa 151
Ser Ser Lys Pro Gly Pro Val Gln Val Val Leu Val Gln Lys Asp Gln

20 25 30 35
cat tcc ttt gag cta gat gag aaa gcc ttg gcc agc atc ctc ttg cag 199
His Ser Phe Glu Leu Asp Glu Lys Ala Leu Ala Ser Ile Leu Leu Gln

25 40 45 50
gac cac atc cga gat ctt gat gtg glg glg gtt tca gtg gct ggt gcc 247
Asp His Ile Arg Asp Leu Asp Val Val Val Val Ser Val Ala Gly Ala

30 55 60 65
ttc cga aag ggc aag tcc ttc att clg gat ttt atg cta cga tac tta 295
Phe Arg Lys Gly Lys Ser Phe Ile Leu Asp Phe Met Leu Arg Tyr Leu

35 70 75 80
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Tyr Ser Gln Lys Glu Ser Gly His Ser Asn Trp Leu Gly Asp Pro Glu

40 85 90 95 100
gaa ccg tta aca gga ttt tcc tgg aga ggg gga tct gat cca gaa acc 391
Glu Pro Leu Thr Gly Phe Ser Trp Arg Gly Gly Ser Asp Pro Glu Thr

45 105 110 115
act ggg att caa atc tgg agt gaa gtt ttc act glg gag aag cca ggt 439

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 10 Gly Lys Lys Val Ala Val Val Leu Met Asp Thr Gln Gly Ala Phe Asp
 135 140 145
 15 agc cag tca act gtc aaa gac tgt gct acc atc ttt gct cta agc act 535
 Ser Gln Ser Thr Val Lys Asp Cys Ala Thr Ile Phe Ala Leu Ser Thr
 150 155 160
 20 atg act agt tct gtt cag att tat aat tta tct cag aac att caa gaa 583
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 25 165 170 175 180
 gat gat ttt caa cag ctg cag ctc ttc aca gaa tac ggt cgt ctg gca 631
 Asp Asp Leu Gln Gln Leu Gln Leu Phe Thr Glu Tyr Gly Arg Leu Ala
 30 185 190 195
 atg gat gaa att ttc caa aag cct ttc cag aca ctg atg ttt ttg gtt 679
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 200 205 210
 40 aga gat tgg agt ttc cct tat gaa tat agc tat gga ctc caa gga gga 727
 Arg Asp Trp Ser Phe Pro Tyr Glu Tyr Ser Tyr Gly Leu Gln Gly Gly
 215 220 225
 45 atg gca ttt ttg gat aag cgt tta cag gtc aag gaa cat caa cat gaa 775
 Met Ala Phe Leu Asp Lys Arg Leu Gln Val Lys Glu His Gln His Glu
 230 235 240
 50 gaa att cag aat gtt cga aat cac att cac tca tgt ttc tcc gat gtc 823
 Glu Ile Gln Asn Val Arg Asn His Ile His Ser Cys Phe Ser Asp Val
 55 245 250 255 260

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	Asp Phe Asp Gly Lys Leu Lys Asp Ile Ala Gly Glu Phe Lys Glu Gln	
	280 285 290	
15	tta cag gca ctg ata ccg tat gta tta aac cca tct aag tta atg gaa	967
	Leu Gln Ala Leu Ile Pro Tyr Val Leu Asn Pro Ser Lys Leu Met Glu	
	295 300 305	
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	Lys Glu Ile Asn Gly Ser Lys Val Thr Cys Arg Gly Leu Leu Glu Tyr	
25	310 315 320	
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	345 350 355	
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	Ala Ser Ala Lys Asp Ile Tyr Tyr Asn Asn Met Glu Glu Val Cys Gly	
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	Gly Glu Lys Pro Tyr Leu Ser Pro Asp Ile Leu Glu Glu Lys His Cys	
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	gaa ttc aaa caa ctt gct ctg gac cat ttt aag aag acc aag aag atg	1255
	Glu Phe Lys Gln Leu Ala Leu Asp His Phe Lys Lys Thr Lys Lys Met	
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 10 atc aag gaa tta tat gag aac ttc tgc aag cac aat ggt agc aag aac 1351
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535

540

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 35 40 45
 Ile Leu Leu Gln Asp His Ile Arg Asp Leu Asp Val Val Val Val Ser
 50 55 60
 Val Ala Gly Ala Phe Arg Lys Gly Lys Ser Phe Ile Leu Asp Phe Met
 65 70 75 80
 40 Leu Arg Tyr Leu Tyr Ser Gln Lys Glu Ser Gly His Ser Asn Trp Leu
 85 90 95
 45 Gly Asp Pro Glu Glu Pro Leu Thr Gly Phe Ser Trp Arg Gly Gly Ser
 100 105 110
 50 Asp Pro Glu Thr Thr Gly Ile Gln Ile Trp Ser Glu Val Phe Thr Val
 115 120 125
 55 Glu Lys Pro Gly Gly Lys Lys Val Ala Val Val Leu Met Asp Thr Gln
 130 135 140

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	Gly	Ala	Phe	Asp	Ser	Gln	Ser	Thr	Val	Lys	Asp	Cys	Ala	Thr	Ile	Phe
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	Ala	Leu	Ser	Thr	Met	Thr	Ser	Ser	Val	Gln	Ile	Tyr	Asn	Leu	Ser	Gln
10						165				170						175
	Asn	Ile	Gln	Glu	Asp	Asp	Leu	Gln	Gln	Leu	Gln	Leu	Phe	Thr	Glu	Tyr
15						180				185						190
	Gly	Arg	Leu	Ala	Met	Asp	Glu	Ile	Phe	Gln	Lys	Pro	Phe	Gln	Thr	Leu
20						195				200						205
	Met	Phe	Leu	Val	Arg	Asp	Trp	Ser	Phe	Pro	Tyr	Glu	Tyr	Ser	Tyr	Gly
25						210				215						220
	Leu	Gln	Gly	Gly	Met	Ala	Phe	Leu	Asp	Lys	Arg	Leu	Gln	Val	Lys	Glu
30	225					230				235						240
	His	Gln	His	Glu	Glu	Ile	Gln	Asn	Val	Arg	Asn	His	Ile	His	Ser	Cys
35						245				250						255
	Phe	Ser	Asp	Val	Thr	Cys	Phe	Leu	Leu	Pro	His	Pro	Gly	Leu	Gln	Val
40						260				265						270
	Ala	Thr	Ser	Pro	Asp	Phe	Asp	Gly	Lys	Leu	Lys	Asp	Ile	Ala	Gly	Glu
45						275				280						285
	Phe	Lys	Glu	Gln	Leu	Gln	Ala	Leu	Ile	Pro	Tyr	Val	Leu	Asn	Pro	Ser
50						290				295						300
	Lys	Leu	Met	Glu	Lys	Glu	Ile	Asn	Gly	Ser	Lys	Val	Thr	Cys	Arg	Gly
55	305					310				315						320
	Leu	Leu	Glu	Tyr	Phe	Lys	Ala	Tyr	Ile	Lys	Ile	Tyr	Gln	Gly	Glu	Asp
						325				330						335
	Leu	Pro	His	Pro	Lys	Ser	Met	Leu	Gln	Ala	Thr	Ala	Glu	Ala	Asn	Asn
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 Glu Lys His Cys Glu Phe Lys Gln Leu Ala Leu Asp His Phe Lys Lys
 385 390 395 400
 15 Thr Lys Lys Met Gly Gly Lys Asp Phe Ser Phe Arg Tyr Gln Gln Glu
 405 410 415
 20 Leu Glu Glu Glu Ile Lys Glu Leu Tyr Glu Asn Phe Cys Lys His Asn
 420 425 430
 Gly Ser Lys Asn Val Phe Ser Thr Phe Arg Thr Pro Ala Val Leu Phe
 25 435 440 445
 Thr Gly Ile Val Ala Leu Tyr Ile Ala Ser Gly Leu Thr Gly Phe Ile
 30 450 455 460
 Gly Leu Glu Val Val Ala Gln Leu Phe Asn Cys Met Val Gly Leu Leu
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 35 Leu Ile Ala Leu Leu Thr Trp Gly Tyr Ile Arg Tyr Ser Gly Gln Tyr
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 40 Arg Glu Leu Gly Gly Ala Ile Asp Phe Gly Ala Ala Tyr Val Leu Glu
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Pro Gly Asp Pro Arg Gln Pro His Arg Pro Asp Pro Gly Arg Pro Val

5 10 15 20

ggc ctg gag cag ctg cgg cgg ctc ggg gtg ctc tac tgg aag ctg gat 152

Gly Leu Glu Gln Leu Arg Arg Leu Gly Val Leu Tyr Trp Lys Leu Asp

25 30 35

gct gac aaa tat gag aat gal cca gaa tta gaa aag atc cga aga gag 200

Ala Asp Lys Tyr Glu Asn Asp Pro Glu Leu Glu Lys Ile Arg Arg Glu

40 45 50

agg aac tac tcc tgg atg gac atc ata acc ata tgc aaa gat aaa cta 248

Arg Asn Tyr Ser Trp Met Asp Ile Ile Thr Ile Cys Lys Asp Lys Leu

55 60 65

cca aat tat gaa gaa aag att aag alg ttc tac gag gag cat ttg cac 296

Pro Asn Tyr Glu Glu Lys Ile Lys Met Phe Tyr Glu Glu His Leu His

70 75 80

ttg gac gat gag atc cgc tac atc ctg gat ggc agt ggg tac ttc gat 344

Leu Asp Asp Glu Ile Arg Tyr Ile Leu Asp Gly Ser Gly Tyr Phe Asp

85 90 95 100

5
 10
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 25
 30
 35
 40
 45
 50
 55

glg agg gac aag gag gac cag lgg atc cgg atc ttc atg gag aag gga 392
 Val Arg Asp Lys Glu Asp Gln Trp Ile Arg Ile Phe Met Glu Lys Gly
 105 110 115
 gac atg glg acg ctc ccc gcg ggg atc tat cac cgc ttc acg glg gac 440
 Asp Met Val Thr Leu Pro Ala Gly Ile Tyr His Arg Phe Thr Val Asp
 120 125 130
 gag aag aac tac acg aag gcc atg cgg ctg ttt glg gga gaa ccg glg 488
 Glu Lys Asn Tyr Thr Lys Ala Met Arg Leu Phe Val Gly Glu Pro Val
 135 140 145
 tgg aca gcg tac aac cgg ccc gct gac cat ttt gaa gcc cgc ggg cag 536
 Trp Thr Ala Tyr Asn Arg Pro Ala Asp His Phe Glu Ala Arg Gly Gln
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 Tyr Val Lys Phe Leu Ala Gln Thr Ala
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 aatttatata tgagctgtgt tagtatittt tcagtgtag atctctggat tcttcacaa 1243

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20 25 30

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35 40 45
 5 Ile Arg Arg Glu Arg Asn Tyr Ser Trp Met Asp Ile Ile Thr Ile Cys
 50 55 60
 10 Lys Asp Lys Leu Pro Asn Tyr Glu Glu Lys Ile Lys Met Phe Tyr Glu
 65 70 75 80
 15 Glu His Leu His Leu Asp Asp Glu Ile Arg Tyr Ile Leu Asp Gly Ser
 85 90 95
 Gly Tyr Phe Asp Val Arg Asp Lys Glu Asp Gln Trp Ile Arg Ile Phe
 100 105 110
 20 Met Glu Lys Gly Asp Met Val Thr Leu Pro Ala Gly Ile Tyr His Arg
 115 120 125
 25 Phe Thr Val Asp Glu Lys Asn Tyr Thr Lys Ala Met Arg Leu Phe Val
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 CCTCCATTTC AGCTAATC ATG GGA GAG ATT AAA GTC TCT CCT GAT TAT AAC 171
 Met Gly Glu Ile Lys Val Ser Pro Asp Tyr Asn
 1 5 10

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5	TGG TTT AGA GGT ACA GTT CCC CTT AAA AAG ATT ATT GTG GAT GAT GAT Trp Phe Arg Gly Thr Val Pro Leu Lys Lys Ile Ile Val Asp Asp Asp 15 20 25	219
10	GAC AGT AAG ATA TGG TCG CTC TAT GAC GCG GGC CCC CGA AGT ATC AGG Asp Ser Lys Ile Trp Ser Leu Tyr Asp Ala Gly Pro Arg Ser Ile Arg 30 35 40	267
15	TGT CCT CTC ATA TTC CTG CCC CCT GTC AGT GGA ACT GCA GAT GTC TTT Cys Pro Leu Ile Phe Leu Pro Pro Val Ser Gly Thr Ala Asp Val Phe 45 50 55	315
20	TTC CGG CAG ATT TTG GCT CTG ACT GGA TGG GGT TAC CGG GTT ATC GCT Phe Arg Gln Ile Leu Ala Leu Thr Gly Trp Gly Tyr Arg Val Ile Ala 60 65 70 75	363
25	TTG CAG TAT CCA GTT TAT TGG GAC CAT CTC GAG TTC TGT GAT GGA TTC Leu Gln Tyr Pro Val Tyr Trp Asp His Leu Glu Phe Cys Asp Gly Phe 80 85 90	411
30	AGA AAA CTT TTA GAC CAT TTA CAA TTG GAT AAA GTT CAT CTT TTT GGC Arg Lys Leu Leu Asp His Leu Gln Leu Asp Lys Val His Leu Phe Gly 95 100 105	459
35	GCT TCT TTG GGA GGC TTT TTG GCC CAG AAA TTT GCT GAA TAT ACT CAC Ala Ser Leu Gly Gly Phe Leu Ala Gln Lys Phe Ala Glu Tyr Thr His 110 115 120	507
40	AAA TCT CCT AGA GTC CAT TCC CTA ATC CTC TGC AAT TCC TTC AGT GAC Lys Ser Pro Arg Val His Ser Leu Ile Leu Cys Asn Ser Phe Ser Asp 125 130 135	555
45	ACC TCT ATC TTC AAC CAA ACT TGG ACT GCA AAC AGC TTT TGG CTG ATG Thr Ser Ile Phe Asn Gln Thr Trp Thr Ala Asn Ser Phe Trp Leu Met 140 145 150 155	603
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	CTA GAA AGT TTG GGT CAG AGT GAA CTG GCT TCA AGA CTT ACC TTG AAT Leu Glu Ser Leu Gly Gln Ser Glu Leu Ala Ser Arg Leu Thr Leu Asn 190 195 200	747
	TGT CAA AAT TCT TAT GTG GTA CCT CAT AAA ATT CGG GAC ATA CCT GTA Cys Gln Asn Ser Tyr Val Val Pro His Lys Ile Arg Asp Ile Pro Val 205 210 215	795

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10	GAA GAA ATG TAC AAG CTG TAT CCT AAT GCC CGA AGA GCT CAT CTG AAA Glu Glu Met Tyr Lys Leu Tyr Pro Asn Ala Arg Arg Ala His Leu Lys 240 245 250	891
15	ACA GGA GGC AAT TTC CCA TAC CTG TGC AGA AGT GCA GAG GTC AAT CTT Thr Gly Gly Asn Phe Pro Tyr Leu Cys Arg Ser Ala Glu Val Asn Leu 255 260 265	939
20	TAT GTA CAG ATA CAT TTG CTG CAA TTC CAT GGA ACC AAA TAC GCG GCC Tyr Val Gln Ile His Leu Leu Gln Phe His Gly Thr Lys Tyr Ala Ala 270 275 280	987
25	ATT GAC CCA TCA ATG GTC AGT GCC GAG GAG CTT GAG GTG CAG AAA GGC Ile Asp Pro Ser Met Val Ser Ala Glu Glu Leu Glu Val Gln Lys Gly 285 290 295	1035
30	AGC CTT GGC ATC AGC CAG GAG GAG CAG TAGTGTGTCT CTCGCTGTCA ATGATGA Ser Leu Gly Ile Ser Gln Glu Glu Gln 300 305	1089
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115 120 125
 His Ser Leu Ile Leu Cys Asn Ser Phe Ser Asp Thr Ser Ile Phe Asn
 130 135 140
 5 Gln Thr Trp Thr Ala Asn Ser Phe Trp Leu Met Pro Ala Phe Met Leu
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 Lys Lys Ile Val Leu Gly Asn Phe Ser Ser Gly Pro Val Asp Pro Met
 165 170 175
 10 Met Ala Asp Ala Ile Asp Phe Met Val Asp Arg Leu Glu Ser Leu Gly
 180 185 190
 Gln Ser Glu Leu Ala Ser Arg Leu Thr Leu Asn Cys Gln Asn Ser Tyr
 195 200 205
 Val Val Pro His Lys Ile Arg Asp Ile Pro Val Thr Ile Met Asp Val
 210 215 220
 15 Phe Asp Gln Ser Ala Leu Ser Thr Glu Ala Lys Glu Glu Met Tyr Lys
 225 230 235 240
 Leu Tyr Pro Asn Ala Arg Arg Ala His Leu Lys Thr Gly Gly Asn Phe
 245 250 255
 20 Pro Tyr Leu Cys Arg Ser Ala Glu Val Asn Leu Tyr Val Gln Ile His
 260 265 270
 Leu Leu Gln Phe His Gly Thr Lys Tyr Ala Ala Ile Asp Pro Ser Met
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 40 AGTGGTCGGA GCCCGCCAGT GGGCAGGCAG CTCTTGCTCA CAGGCCGCGG TGCCCAAGGCC 180
 GCTGGCTCTC CGCAGGGCGG A ATG GCG CTG CAA GTG GAG CTG GTA CCC ACC 231
 Met Ala Leu Gln Val Glu Leu Val Pro Thr
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 Gly Glu Ile Ile Arg Val Val His Pro His Arg Pro Cys Lys Leu Ala
 15 20 25
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 50 Leu Gly Ser Asp Gly Val Arg Val Thr Met Glu Ser Ala Leu Thr Ala
 30 35 40
 CGT GAC CGG GTG GGG GTG CAG GAT TTC GTG CTG CTG GAG AAC TTC ACC 375
 55 Arg Asp Arg Val Gly Val Gln Asp Phe Val Leu Leu Glu Asn Phe Thr
 45 50 55

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10	CTC ATC TAC ACC TAC ATT GGC CCC GTC CTG GTC TCT GTC AAT CCC TAC Leu Ile Tyr Thr Tyr Ile Gly Pro Val Leu Val Ser Val Asn Pro Tyr 75 80 85 90	471
15	CGG GAC CTG CAG ATC TAC AGC CGG CAG CAT ATG GAG CGT TAC CGT GGC Arg Asp Leu Gln Ile Tyr Ser Arg Gln His Met Glu Arg Tyr Arg Gly 95 100 105	519
20	GTC AGC TTC TAT GAA GTG CCC CCT CAC CTG TTT GCC GTG GCG GAC ACT Val Ser Phe Tyr Glu Val Pro Pro His Leu Phe Ala Val Ala Asp Thr 110 115 120	567
25	GTG TAC CGA GCA CTG CGC ACG GAG CGT CGG GAC CAG GCT GTG ATG ATC Val Tyr Arg Ala Leu Arg Thr Glu Arg Arg Asp Gln Ala Val Met Ile 125 130 135	615
30	TCT GGG GAG AGC GGG GCA GGC AAG ACC GAG GCC ACC AAG AGG CTG CTG Ser Gly Glu Ser Gly Ala Gly Lys Thr Glu Ala Thr Lys Arg Leu Leu 140 145 150	663
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45	GCC AAG ACC CTC CGG AAC GAT AAC TCC AGC AGG TTC GGG AAG TAC ATG Ala Lys Thr Leu Arg Asn Asp Asn Ser Ser Arg Phe Gly Lys Tyr Met 190 195 200	807
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65	CTC TTC GCA GGC TGG GCT TGG AAC GGA ACC CCC AGA GCT ATC TGT ACC Leu Phe Ala Gly Trp Ala Trp Asn Gly Thr Pro Arg Ala Ile Cys Thr 255 260 265	999
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Trp

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	TCGTGGCCAG CGTCCITCAT TTGGGCAACA TCCACTTTGC TGCCAACGAG GAGAGCAATG	1178
	CCCAGGTCAC CACCGAGAAC CAGCTCAAGT ATCTGAGCCC ATTCAGTATG CGGTGCCTGT	1238
	TGTGAAATAC GACCGCAAGG GCTACAAGCC TCGCTCCCGG CAGCTGCTGC TCACGCCCAA	1298
	CGCCGTCGTC ATCGTGGAGG ACGCCAAAGT CAAGCAGAGG ATTGATTACG CCAACCTGAC	1358
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	CAATAAGCAA AAGGGAGATG TGGTGTGCA GAGTGACCAC GTGATTGAGA CGCTGACCAA	1478
	GACAGCCCTC AGTGCCCAACC GCGTGAACAG CATCAACATC AACCAGGGCA GCATCACGTT	1538
	TGCAGGGGGC CCCGGCAGGG ATGGCACCAT TGACTTCACA CCCGGCTCGG AGCTGCTCAT	1598
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25	AGAATGTCTT TTTAGGCTGG GCATGCTGGC TCACGCCTGT AACCCAGCA CTTTGGGAGG	2318
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	35 40 45	
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	100 105 110	
	Pro Pro His Leu Phe Ala Val Ala Asp Thr Val Tyr Arg Ala Leu Arg	
	115 120 125	
	Thr Glu Arg Arg Asp Gln Ala Val Met Ile Ser Gly Glu Ser Gly Ala	
55	130 135 140	
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	145		150		155		160									
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			5					10					15			
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	Pro	Arg	His	Ser	Thr	His	Met	Ala	Ser	Gly	Val	Gly	Ala	Ala	Phe	Glu
			20				25					30				
45	GAA	CTG	CCT	CAC	GAC	GGC	ACG	TGT	GAC	GAG	TGC	GAG	CCC	GAC	GAG	GCT
	Glu	Leu	Pro	His	Asp	Gly	Thr	Cys	Asp	Glu	Cys	Glu	Pro	Asp	Glu	Ala
		35					40					45				
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		50				55				60					65	
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				70					75						80	
60	GAA	TAC	GTC	CAC	GGC	TCC	CAG	GCC	TGG	ACC	CCG	CCA	GCT	GAC	GGA	GAG
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25	AGC GAG GCC GAA GAA GAC AAC CAA GAA GAA GGG GAA TCC GAG GCG GAG Ser Glu Ala Glu Glu Asp Asn Gln Glu Glu Gly Glu Ser Glu Ala Glu 165 170 175	646
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5 ATC CAA TCC CAC ATG GAT AGG TTG ATG ACT CAG ATG GCC CAA GCC AAG 1126
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Ala Pro Gly Ala Glu Glu Val Cys Arg Glu Cys Gly Phe Cys Tyr Cys
50 55 60
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 130 135 140
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 145 150 155 160
 15 Glu Ser Glu Ala Glu Glu Asp Asn Gln Glu Glu Gly Glu Ser Glu Ala
 165 170 175
 Glu Gly Glu Thr Glu Ala Glu Ser Glu Phe Asp Pro Glu Ile Glu Met
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 195 200 205
 20 Leu Ser Thr Tyr Cys Gln Glu Asp Arg Gln Leu Ile Cys Val Leu Cys
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 Pro Val Ile Gly Ala His Gln Gly His Gln Leu Ser Thr Leu Asp Glu
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 25 Ala Phe Glu Glu Leu Arg Ser Lys Asp Ser Gly Gly Leu Lys Ala Ala
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 Met Ile Glu Leu Val Glu Arg Leu Lys Phe Lys Ser Ser Asp Pro Lys
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<220>

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26

Claims

1. A DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:143, 145, 147, 149, 151, 153, 155, 157, 168, 170 and 172.
2. A shear stress-responsive DNA capable of hybridizing with a DNA having the nucleotide sequences represented by SEQ ID NO:143, 145, 149, 151, 153, 155, 157, 168, 170 or 172 under stringent conditions.
3. A shear stress-responsive DNA capable of hybridizing with a DNA having the nucleotide sequence represented by SEQ ID NO:147 under stringent conditions, and having not less than 90% homology with the DNA.
4. A DNA having the same sequence as 5 to 60 consecutive bases in a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:143, 145, 149, 153, 155, 157, 168, 170 and 172, or a DNA having a sequence complementary to the DNA.
5. A method for detecting an mRNA for a shear stress-responsive gene using a DNA according to any one of claims 1 to 4.
6. A diagnostic agent for vascular diseases caused by arteriosclerosis which contains a DNA according to any one of claims 1 to 4.
7. A method for detecting a gene causative of arteriosclerosis using a DNA according to any one of claims 1 to 4.
8. A method for screening an agent for regulating the transcription or translation of a shear stress-responsive gene using a DNA according to any one of claims 1 to 4.
9. A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using a DNA according to any one of claims 1 to 4.
10. A therapeutic agent for vascular diseases caused by arteriosclerosis which contains a DNA according to any one of claims 1 to 4.
11. A recombinant virus vector containing a DNA according to any one of claims 1 to 4.
12. A recombinant virus vector containing an RNA comprising a sequence homologous with the sense strand of a DNA according to any one of claims 1 to 4.
13. A DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO: 111, 113, 115, 116, 117, 119, 121, 123, 125, 127, 129, 130, 131, 132, 133, 134, 135, 137, 139 and 141.
14. A shear stress-responsive DNA capable of hybridizing with the DNA according to claim 13 under stringent condi-

tions.

15. A DNA having the same sequence as 5 to 60 consecutive bases in a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:111, 113, 115, 116, 117, 119, 121, 123, 125, 127, 129, 130, 131, 132, 133, 134, 135, 137, 139 and 141, or a DNA having a sequence complementary to the DNA.
16. A diagnostic agent for vascular diseases caused by arteriosclerosis which contains a DNA according to any one of claims 13 to 15.
17. A method for detecting a gene causative of arteriosclerosis using a DNA according to any one of claims 13 to 15.
18. A method for screening an agent for regulating the transcription or translation of a shear stress-responsive gene using a DNA according to any one of claims 13 to 15.
19. A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using a DNA according to any one of claims 13 to 15.
20. A method for detecting an mRNA for a shear stress-responsive gene using a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.
21. A method for identifying the apoptosis sensitivity of cells by detecting the endogenous transcription level of a DNA having the nucleotide sequence represented by SEQ ID NO:7 using a DNA having the nucleotide sequence represented by SEQ ID NO:7 or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7.
22. A method for suppressing or promoting the apoptosis of cells by regulating the endogenous transcription or translation of a DNA having the nucleotide sequence represented by SEQ ID NO:7 using a DNA having the nucleotide sequence represented by SEQ ID NO:7 or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7, or an antisense DNA having a nucleotide sequence complementary to the nucleotide sequence of each of these DNAs.
23. A diagnostic agent for vascular diseases caused by arteriosclerosis which contains a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.
24. An agent for identifying the apoptosis sensitivity of cells which contains a DNA having the nucleotide sequence represented by SEQ ID NO:7, or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7.
25. A method for screening an agent for regulating the transcription or translation of a shear stress-responsive gene using a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.
26. A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.
27. A method for screening an agent for suppressing or promoting the apoptosis of cells by regulating the endogenous transcription or translation of a DNA having the nucleotide sequence represented by SEQ ID NO:7 using a DNA having the nucleotide sequence represented by SEQ ID NO:7 or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7.
28. A therapeutic agent for vascular diseases caused by arteriosclerosis which contains a DNA having a nucleotide

sequence selected from the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.

- 5 29. An agent for suppressing or promoting the apoptosis of cells which contains a DNA having the nucleotide sequence represented by SEQ ID NO:7 or a DNA having the same sequence as 5 to 60 consecutive bases in the nucleotide sequence represented by SEQ ID NO:7, or an antisense DNA having a nucleotide sequence complementary to the nucleotide sequence of each of these DNAs.
- 10 30. A recombinant virus vector containing a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.
- 15 31. A recombinant virus vector containing an RNA comprising a sequence homologous with the sense strand of a DNA having a nucleotide sequence selected from the nucleotide sequences represented by SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109.
- 20 32. A therapeutic agent for vascular diseases caused by arteriosclerosis which contains a recombinant virus vector according to claim 30 or 31.
33. A method for suppressing the apoptosis of cells using a recombinant virus vector containing a DNA having the nucleotide sequence represented by SEQ ID NO:7, or a recombinant virus vector containing an RNA comprising
25 a sequence homologous with the sense strand of a DNA having the nucleotide sequence represented by SEQ ID NO:7.
34. A method for screening an agent for suppressing or promoting the apoptosis of cells using a recombinant virus vector containing a DNA having the nucleotide sequence represented by SEQ ID NO:7, or a recombinant virus vector containing an RNA comprising a sequence homologous with the sense strand of a DNA having the nucleotide
30 sequence represented by SEQ ID NO:7.
35. A protein having an amino acid sequence selected from the amino acid sequences represented by SEQ ID NO: 144, 146, 148, 150, 152, 154, 156, 158, 169, 171 and 173.
35
36. A protein comprising an amino acid sequence in which one or more amino acids are deleted, replaced or added as compared with the amino acid sequence possessed by the protein according to claim 35, and having an activity participating in the formation of an arteriosclerotic lesion.
- 40 37. A DNA encoding a protein according to claim 35 or 36.
38. A recombinant DNA obtained by inserting a DNA according to any one of claims 1-4 and 37 into a vector.
39. A transformant obtained by introducing the recombinant DNA according to claim 38 into a host cell.
45
40. A process for the preparation of a protein which comprises culturing the transformant according to claim 39 in a culture medium, causing a protein according to claim 35 or 36 to be produced and accumulated in the culture medium, and harvesting the protein from the resulting culture.
- 50 41. A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis which comprises culturing the transformant according to claim 39 in a culture medium and using the resulting culture for the screening.
- 55 42. A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using a protein according to claim 35 or 36.
43. A recombinant virus vector capable of producing a protein according to claim 35 or 36.

44. A therapeutic agent for vascular diseases caused by arteriosclerosis which contains the recombinant virus vector of claim 43.
45. An antibody capable of recognizing a protein according to claim 35 or 36.
46. A method for detecting a protein according to claim 35 or 36 immunologically, using the antibody according to claim 45.
47. A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using the antibody according to claim 45.
48. A method for screening an agent for regulating the transcription or translation of a shear stress-responsive gene using the antibody according to claim 45.
49. A diagnostic agent for vascular diseases caused by arteriosclerosis which contains the antibody according to claim 45.
50. A therapeutic agent for vascular diseases caused by arteriosclerosis which contains the antibody according to claim 45.
51. A drug delivery method which comprises combining the antibody of claim 45 with a radioactive isotope, a protein or a low-molecular-weight agent, and delivering the resulting conjugated antibody to an arteriosclerotic lesion.
52. An antibody capable of recognizing a protein having an amino acid sequence represented by SEQ ID NO: 112, 114, 118, 120, 122, 124, 126, 128, 136, 138, 140 and 142.
53. A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using the antibody according to claim 52.
54. A method for screening an agent for suppressing the transcription or translation of a shear stress-responsive gene using the antibody according to claim 52.
55. A diagnostic agent for vascular diseases caused by arteriosclerosis which contains the antibody according to claim 52.
56. A therapeutic agent for vascular diseases caused by arteriosclerosis which contains the antibody according to claim 52.
57. A drug delivery method which comprises combining the antibody of claim 52 with a radioactive isotope, a protein or a low-molecular-weight agent, and delivering the resulting conjugated antibody to an arteriosclerotic lesion.
58. A method for screening an agent capable of binding specifically to a protein having the amino acid sequence represented by SEQ ID NO:8 and effective for suppressing or promoting the apoptosis of cells, using a protein having the amino acid sequence represented by SEQ ID NO:8.
59. A method for screening an agent for suppressing or promoting the apoptosis of cells which comprises inserting a DNA having the nucleotide sequence represented by SEQ ID NO:7 or a DNA encoding a protein having the amino acid sequence represented by SEQ ID NO:8, into a vector; introducing the resulting recombinant DNA into a host cell; culturing the resulting transformant in a culture medium; and using the resulting culture for the screening.
60. A recombinant virus vector capable of producing a protein having an amino acid sequence selected from the amino acid sequences represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 and 110.
61. A therapeutic agent for vascular diseases caused by arteriosclerosis which contains the recombinant virus vector according to claim 60.

62. A method for suppressing the apoptosis of cells using a recombinant virus vector capable of producing a protein having the amino acid sequence represented by SEQ ID NO:8.
- 5 63. An agent for suppressing the apoptosis of cells which contains a recombinant virus vector capable of producing a protein having the amino acid sequence represented by SEQ ID NO:8.
- 10 64. A method for screening a therapeutic agent for vascular diseases caused by arteriosclerosis using an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 or 110.
- 15 65. A method for screening an agent for suppressing or promoting the transcription or translation of a shear stress-responsive gene using an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 or 110.
- 20 66. A method for regulating the apoptosis of cells using an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.
- 25 67. A method for screening an agent for regulating the apoptosis of cells using an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.
68. A method for identifying the apoptosis sensitivity of cells by detecting the expression level of a protein having the amino acid sequence represented by SEQ ID NO:8 using an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.
69. A method according to any one of claims 21, 22, 27, 33, 34, 58, 59, 62, 66, 67 and 68 wherein the cells are vascular endothelial cells.
- 30 70. A diagnostic agent for vascular diseases caused by arteriosclerosis which contains an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 or 110.
- 35 71. An agent for identifying the apoptosis sensitivity of cells which contains an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.
- 40 72. A therapeutic agent for vascular diseases caused by arteriosclerosis which contains an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 or 110.
- 45 73. An agent for regulating the apoptosis of cells which comprises an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:8.
74. An agent for suppressing or promoting the apoptosis of cells which is obtained by a method according to any one of claims 27, 34, 58, 59 and 67.
- 50 75. An agent according to any one of claims 24, 29, 63, 71, 73 and 74 wherein the cells are vascular endothelial cells.
- 55 76. A drug delivery method which comprises combining an antibody capable of recognizing a protein having the amino acid sequence represented by SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 or 110, with a radioactive isotope, a protein or a low-molecular-weight agent, and delivering the resulting conjugated antibody to an arteriosclerotic lesion.

FIG.1

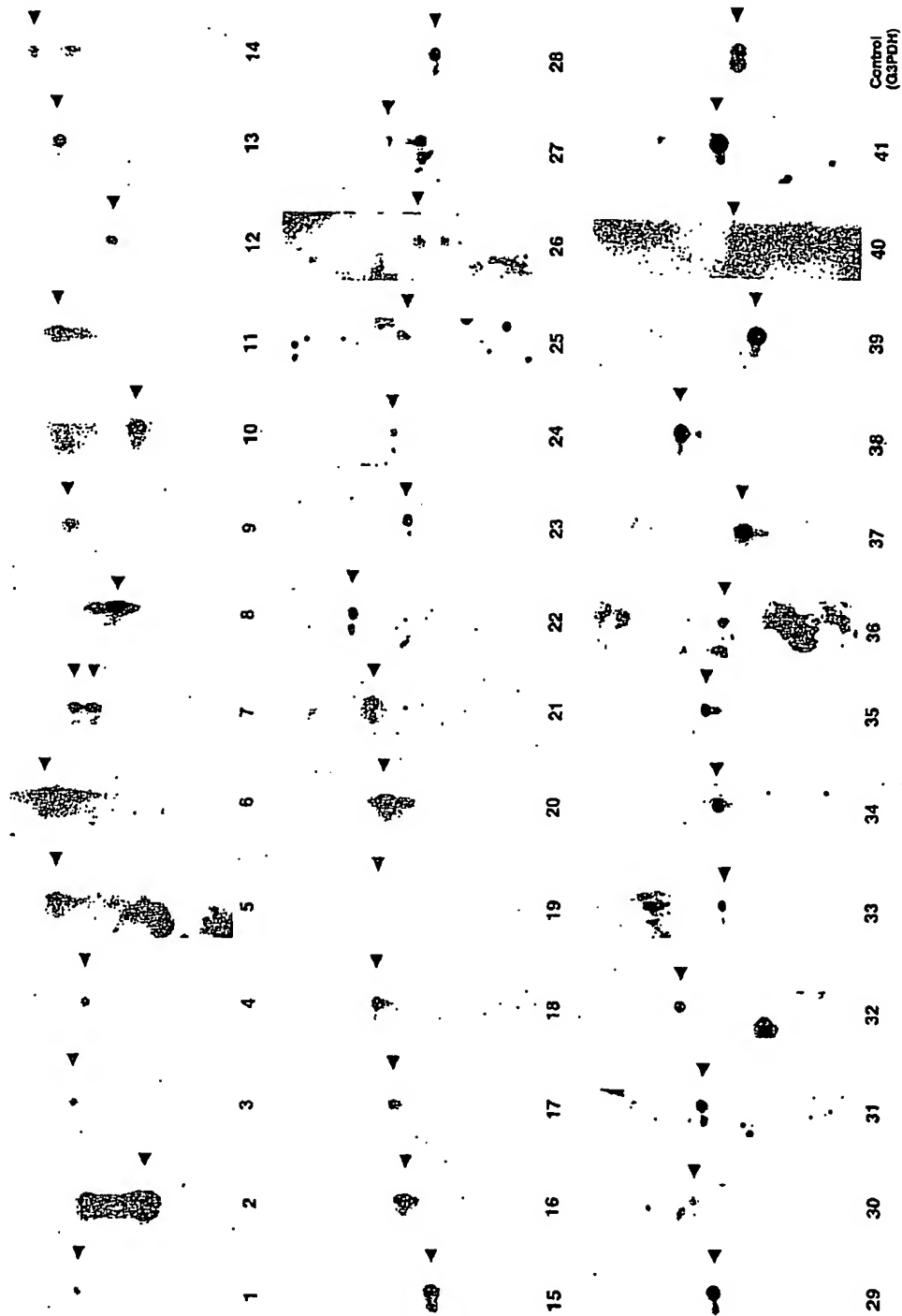


FIG.2

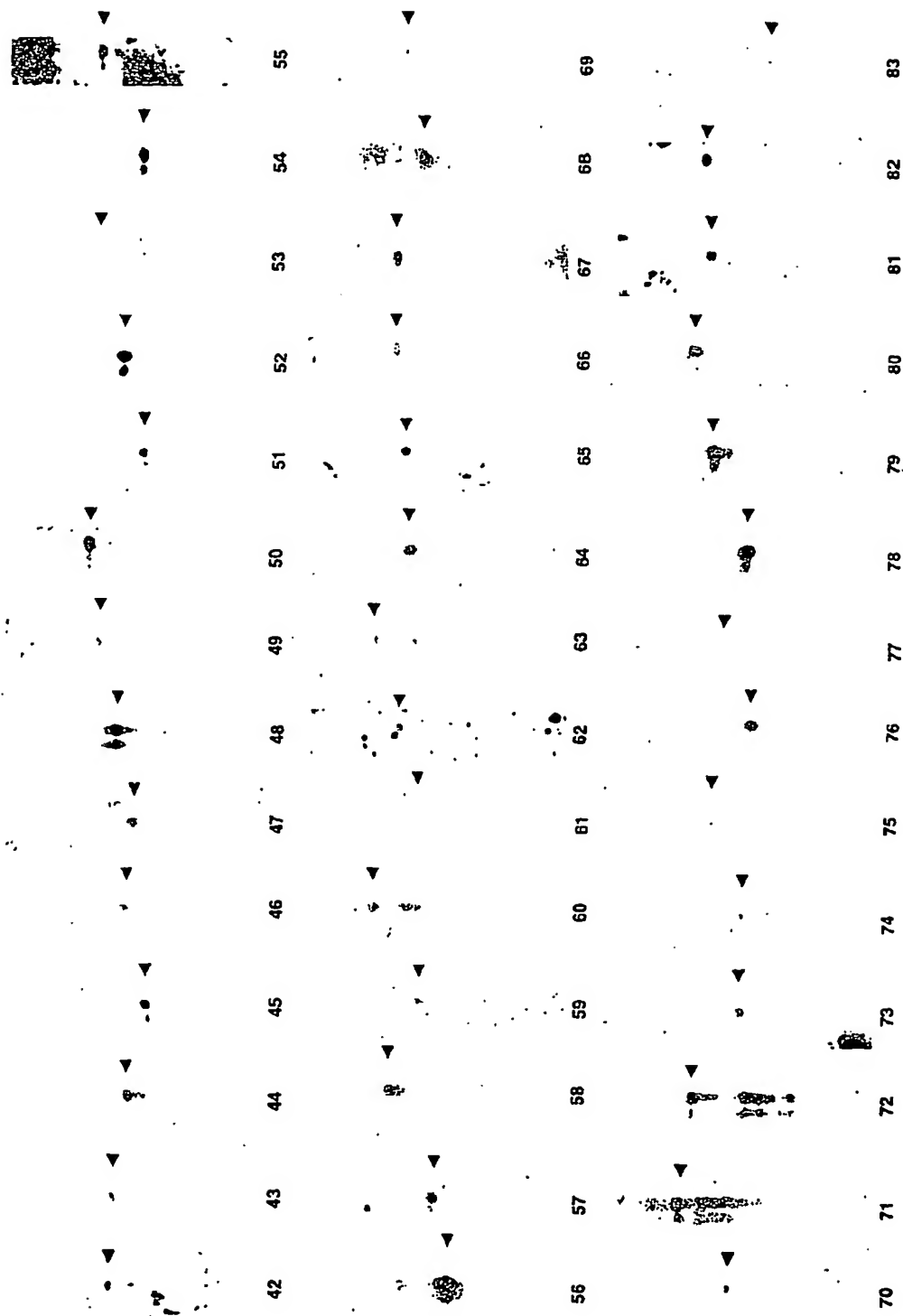


FIG.3

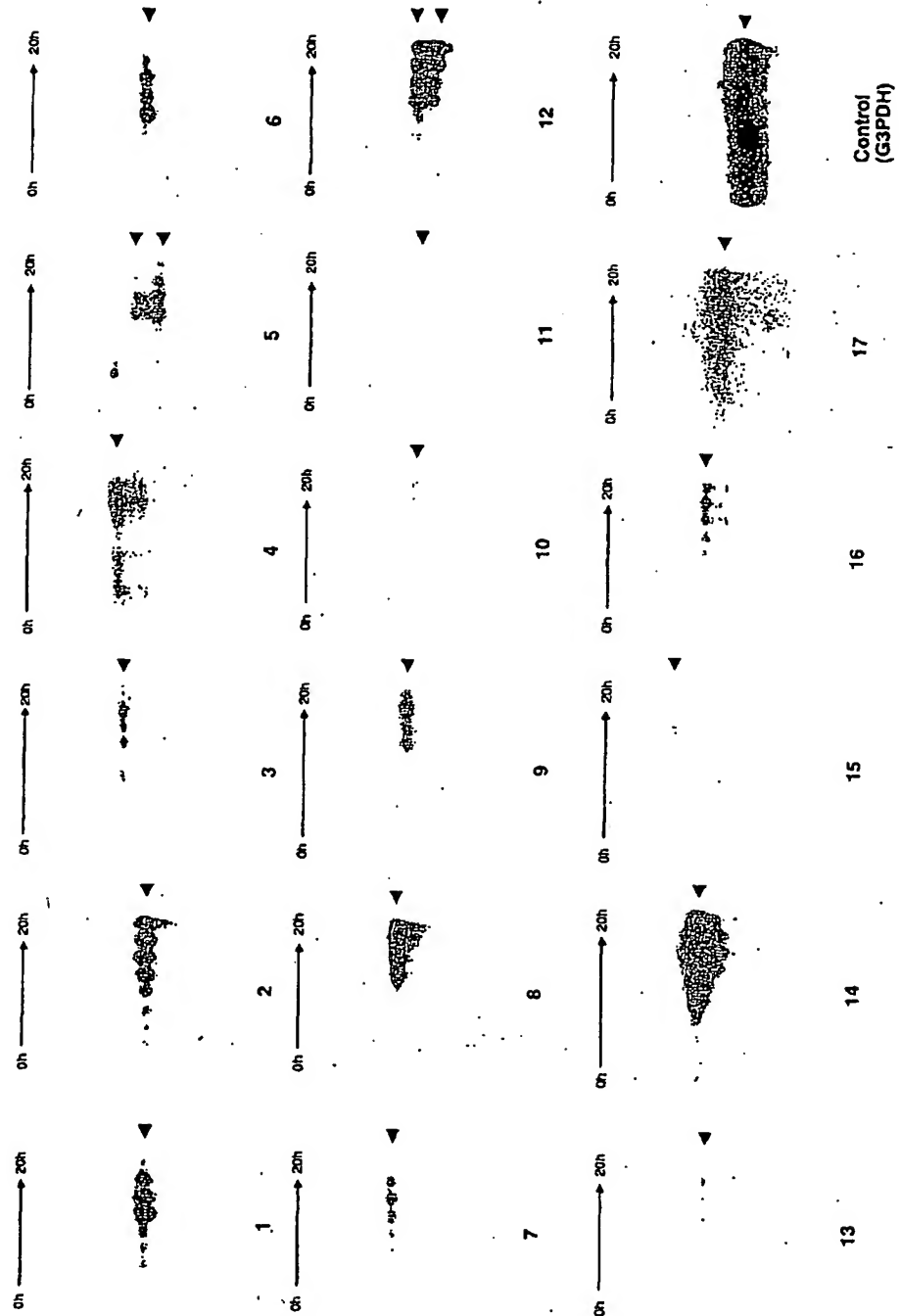


FIG.4



FIG. 5

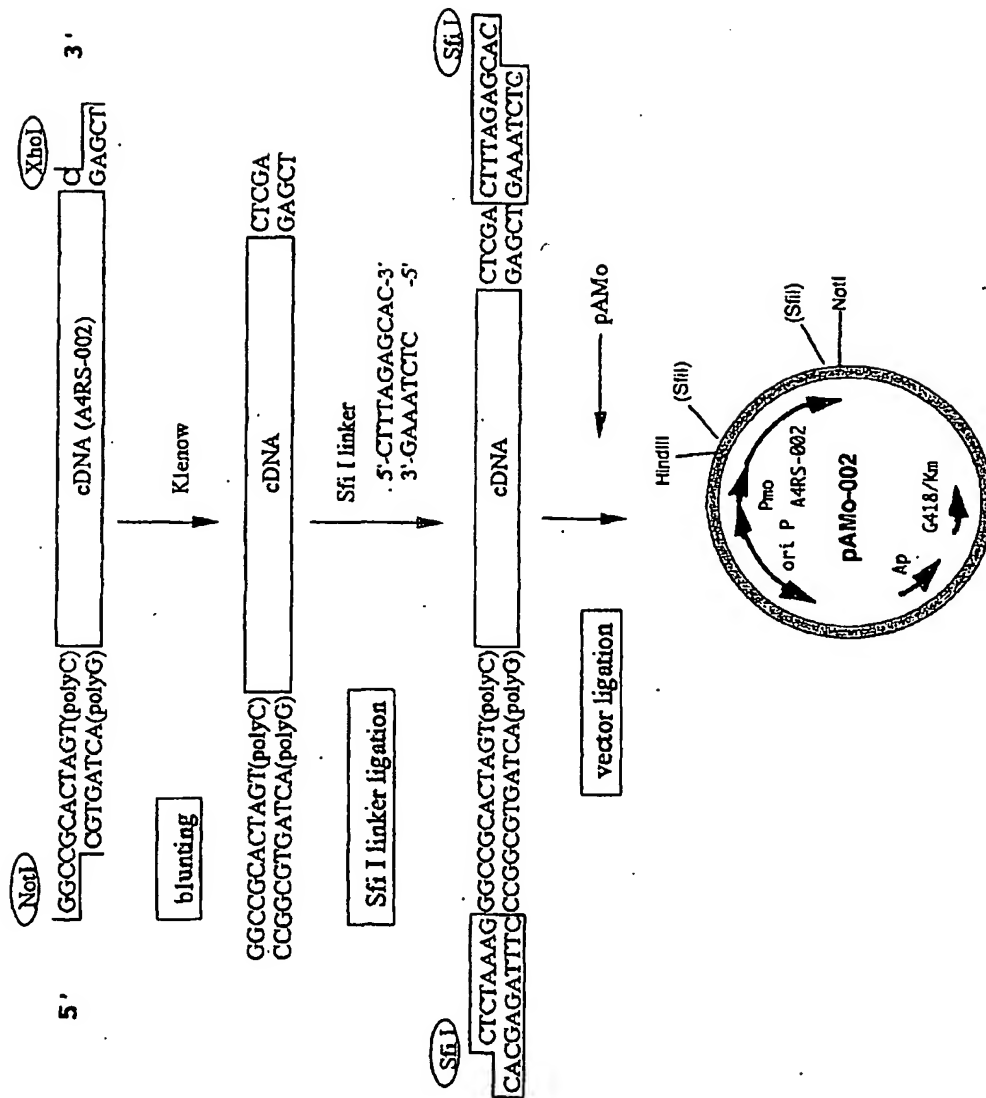


FIG.6A

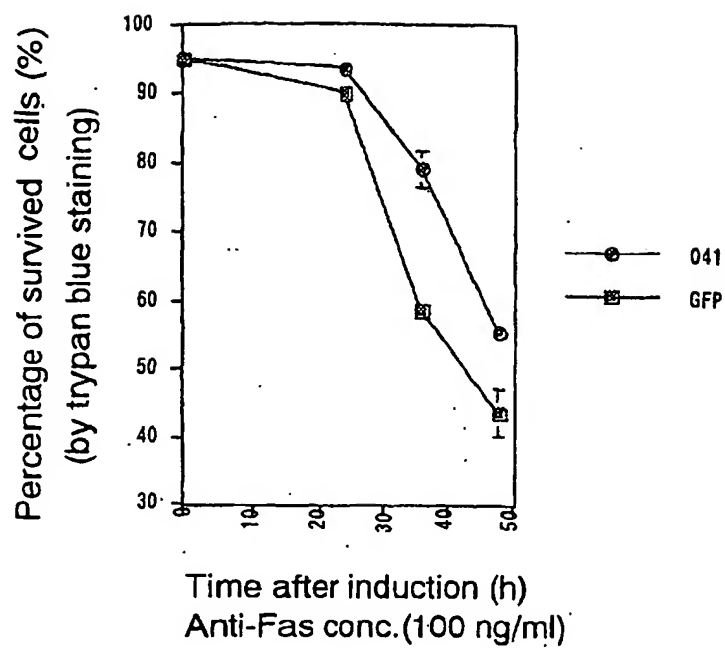


FIG.6B

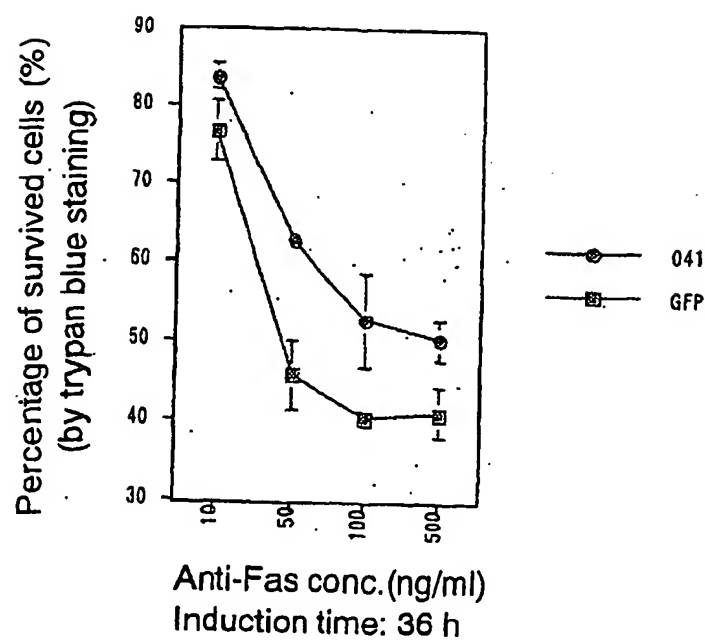


FIG.7A

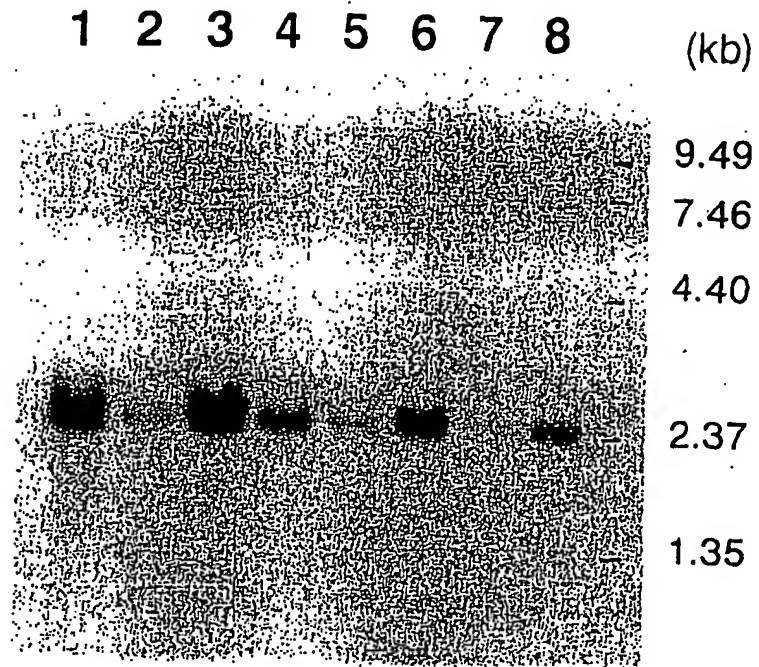


FIG.7B

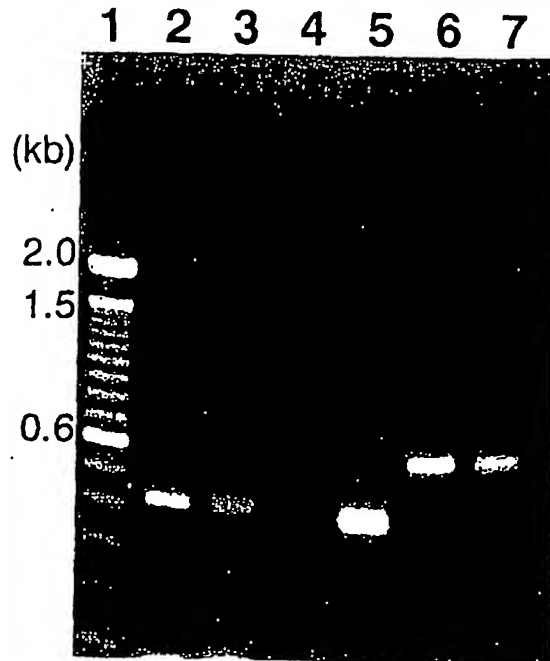


FIG.8

A4RS-041

LFG

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1 MSNPSAPPYEDRNPLYPGPLPPGGYGQPSV.....LPGGYPAYPGYPQ 44
  | | | | | | | | | | | | | | | | | | | | | | | | | | | |
1 .....MTRGKLSVANKAPGTEGQQQVHGEKKEAPVPSAPPSYEE 40

45 ..PGYGHYPAGYPQMP...PTHMPMPNYGP..GHGYDGEERAVSDSFGP. 86
  | | | | | | | | | | | | | | | | | | | | | | | | | | | |
41 ATSGEGMKAGAFPAPTAVPLHPSWAYVDPSSSSSYDNGFPPEMTMSSSPL 90

87 GEWDDRKVRHTFIRKVSIIISVQLLITVAIIAIFTFVEPVSAFRRNVAV 136
  : | | | | | | | | | | | | | | | | | | | | | | | | | | | |
91 SAGMTKKVRRVVRKVYTILLIQLLVTLAVVALFTFCDPCQGLCSGQPGW 140

137 YYVSYAVFVVTYLILACCGPRRRFPWNIIILLTFTFAMGFMGTISSMY 186
  | : | | | | | | | | | | | | | | | | | | | | | | | | | | | |
141 YWASYAVFFATYLTACCSGPRRHFPWNIIILLTVFTLSMAYLTGMLSSYY 190

187 QTKAVIIAMIITAVVISVTIFCFQTKVDFTSCTGLFCVLGIVLLVTGIV 236
  | . | : : | | | | | : | | | | | | | | | | | | | | | | | : :
191 NTTSVLLCLGITALVCLSVTVFSFQTKDFDFTSCQGVLFVLLMTLFFSGLI 240

237 TSIVLYFQYVYWLHMLYAALGAICFTLFLAYDTQLVLGNRKHTISPEDI 286
  . | . | | | | | | | | | | | | | | | | | | | | | | | | | | |
241 LAILLPFQYVPWLHAVYAALGAGVFTLFLALDTQLLMGNRRHSLSPPEEYI 290

287 TGALQIYTDIIYIFTFVLQLMGDRN. 311
  | | | | | | | | | | | | | | | | | | | | | | | | | | | |
291 FGALNIYLDIIYIFTFFLQLFGTNR 316

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/06840

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl⁷ C12N15/12, C07K14/435, 16/18, C12P21/02,
C12Q1/68, A61K38/00, 39/395, 48/00, A61P9/10,
G01N33/50, 33/53,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl⁷ C12N15/11-15/62, C07K14/00-14/825

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
GenBank/EMBL/DDBJ/GeneSeq, SwissProt/PIR/GeneSeq,
BIOSIS (DIALOG), WPI (DIALOG)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, 99/14327, A2 (GENENTECH, INC.), 25 March, 1999 (25.03.99), especially, PRO246, FIG.26 (Accession No.X28436), FIG.27 (Accession No.Y05286) & AU, 9893121, A & ZA, 9808293, A	2, 4, 11, 12, 36-40, 43, 45, 46
X	WO, 99/14328, A2 (GENENTECH, INC.), 25 March, 1999 (25.03.99), especially, FIGURE 16 (Accession No.X52221), FIGURE 17 (Accession No.Y13351) & ZA, 9808460, A & AU, 9893178, A & EP, 1027434, A2	2, 4, 11, 12, 36-40, 43, 45, 46
X	US, 5942606, A (INCYTE PHARMACEUTICALS, INC.), 24 August, 1999 (24.08.99), especially, SEQ ID NO:2 (Accession No.X87000), SEQ ID NO:1 (Accession No.Y27096) (Family: none)	2, 4, 11, 12, 36-40, 43, 45, 46
P, X	WO, 99/58660, A1 (HUMAN GENOME SCIENCES, INC.), 18 November, 1999 (18.11.99),	2, 4, 11, 12, 36-40, 43,

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
19 December, 2000 (19.12.00)

Date of mailing of the international search report
26 December, 2000 (26.12.00)

Name and mailing address of the ISA/
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/06840

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	especially, SEQ ID NO:39 (Accession No.Z65278), SEQ ID NO:291 (Accession No.Y76303) & AU, 9938831, A	45,46
P,X	WO, 00/11015, A1 (ALPHAGENE, INC.), 02 March, 2000 (02.03.00), especially, SEQ ID NO:37 (Accession No.A23441), SEQ ID NO:38 (Accession No.Y94999) & AU, 9957847, A	2,4,11,12, 36-40,43, 45,46
P,X	WO, 00/15666, A2 (GENENTECH, INC.), 23 March, 2000 (23.03.00), especially, FIGURE 15 (Accession No.A30052), FIGURE 16 (Accession No.Y88574) & AU, 9958167, A	2,4,11,12, 36-40,43, 45,46
A	TOPPER, James N. et al., "Blood flow and vascular gene expression: fluid shear stress as a modulator of endothelial phenotype", Molecular Medicine Today, January, 1999, Volume 5, Number 1, pages 40-46	1,2,4-12, 35-50
A	ANDO, Joji et al., "Flow-dependent Regulation of Gene Expression in Vascular Endothelial Cells", Japanese Heart Journal, January, 1996, Volume 37, Number 1, 19-32	1,2,4-12, 35-50

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/06840

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1.
- ☒
- Claims Nos.: 22,33,51,57,66,69,76

because they relate to subject matter not required to be searched by this Authority, namely:

The inventions as set forth in claims 22, 33, 66 and 69 relate to "methods for inhibiting, promoting or controlling cell apoptosis". As stated in the description, these methods are performed for therapy in the human body. Therefore, these inventions pertain to methods for treatment of the human body by therapy. The inventions as set forth in claims 51, 57 and 76 relate to "drug delivery methods for inducing a fused antibody comprising an antibody bonded to a drug into arteriosclerotic focus" which are to be performed in the human body in therapy. Therefore, these inventions pertain to methods for treatment of the human body by therapy.

- 2.
- ☐
- Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3.
- ☐
- Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

- 4.
- ☒
- No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

The inventions as set forth in claims which relate to the base sequence represented by SEQ ID NO:143 or the amino acid sequence represented by SEQ ID NO:144

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/06840

Continuation of Box No.II of continuation of first sheet(1)

The requirement of unity of invention in international application (PCT Rule 13.1) is not satisfied unless there is a technical relationship between a group of inventions as set forth in claims involving one or more of the same or corresponding special technical feature. The term "special technical feature" means a technical feature clearly showing the contribution achieved by the inventions as set forth in the claims as a whole (PCT Rule 13.2). The requirement of unity of invention is judged without considering whether the group of inventions are described in separate claims or in a single claim in the alternative form (PCT Rule 13.3).

In the present case, the inventions relating to the base sequences represented by SEQ ID NOS: 143, 145, 147, 149, 151, 153, 155, 157, 168, 170, 172, 111, 113, 117, 119, 121, 123, 125, 127, 135, 137, 139, 141, 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109 (or the amino acid sequences represented by SEQ ID NOS: 144, 146, 148, 150, 152, 154, 156, 158, 169, 171, 173, 112, 114, 118, 120, 122, 124, 126, 128, 136, 138, 140, 142, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 and 110) or the base sequences represented by SEQ ID NO: 115, 116, 129, 130, 131, 132, 133 and 134 have a matter in common "DNA the expression of which is induced by a shear stress stimulus in hemoendothelial cells". However, there had been publicly known endothelin-1, monocyte chemotactic protein-1, etc. as "DNA the expression of which is induced by a shear stress stimulus in hemoendothelial cells", as the applicant recognizes. Therefore, it can be concluded that there is no "special technical feature" common to the inventions relating to the above-described base sequences (or amino acid sequences) as set forth in the claims.

Such being the case, the claims involve 86 separate inventions respectively relating to the base sequences represented by SEQ ID NOS: 143, 145, 147, 149, 151, 153, 155, 157, 168, 170, 172, 111, 113, 117, 119, 121, 123, 125, 127, 135, 137, 139, 141, 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107 and 109 (or the amino acid sequences represented by SEQ ID NOS: 144, 146, 148, 150, 152, 154, 156, 158, 169, 171, 173, 112, 114, 118, 120, 122, 124, 126, 128, 136, 138, 140, 142, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 and 110) or the base sequences represented by SEQ ID NO: 115, 116, 129, 130, 131, 132, 133 and 134.